Pregnancy and Psychopathology

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Voor mijn ouders,

mijn beide zusjes,

en mijn grote liefde, Lianne

CONTENTS

CHAPTER 1

General introduction

T. Verbeek

For a lot of people, because of the joy and happiness of a new life, pregnancy means being on cloud nine. However, the general population may not be aware that this does not apply to every woman. Psychopathology around pregnancy should not be underrated. For as many as 10-20% of all pregnant women, pregnancy results in black clouds, gathering over them.[1,2]

This thesis will discuss different aspects of psychopathology around pregnancy. In the first part, consequences of anxiety and depression for the offspring as well as risk factors will be elucidated, using studies in the Netherlands and abroad. In the second part, effects of treatment of antenatal anxiety and depression using cognitive behavioural therapy on symptom level, perinatal outcomes, child development, and child behaviour when compared to care as usual will be assessed.

Consequences of anxiety and depression

Guilt, hopelessness, worthlessness, stress and excessive worries are examples of symptoms of anxiety and depression during or after pregnancy. Whether or not related to the pregnancy or the baby, these symptoms are associated with a range of adverse outcomes for mother and child. Parts of this thesis focus on their effects on breastfeeding and long-term effects on mental health in the offspring.

Symptoms of anxiety and depression not only cause uncomfortable feelings, but may also adversely affect the overall health of women.[3] Anxiety and depression are associated with numerous diseases including coronary heart disease,[4,5] diabetes mellitus,[6,7] stroke,[8,9] and even Parkinson's disease.[10] A recent review demonstrated that the pooled relative risk of all-cause mortality among those with mental disorders was 2.22 and concluded that mental disorders, especially anxiety and depression, rank among the most substantial causes of death worldwide.[11]

As for the child, long before birth, the adverse effects of the psychopathology of an antenatally anxious or depressed woman on her offspring may commence. Indeed, there is ample evidence that symptoms of anxiety and depression have adverse effects on perinatal outcomes[12,13] and cognitive, motor and psychosocial development of the offspring.[14-20] There are several theoretically possible mechanisms through which depression or anxiety during pregnancy could have an adverse effect on the offspring. These can be divided into direct and indirect.

A *direct* mechanism is one in which depression and/or anxiety activates the maternal stress system, leading to elevated glucocorticoid levels. Subsequently, this may influence the development and long-term physiology of the foetus' brain by passing the placenta. This direct mechanism is called "early life programming" or Barker's theory and is a hypothesis for the

(partial) explanation of brain disorders and cardiovascular disease in the offspring.[21,22] In this theory, it is stated that maternal hormones and other substances influence the body and mind of a foetus in utero, and that the foetus' body is adapted due to this influence. This adaptation is posed to be long-term.[22] Furthermore, epigenetic variation(s) have been proposed as a mechanism in linking early life exposures to long-term psychological and behavioural outcomes.[23]

The effect of maternal stress on the developing foetus may also be (partly) *indirect*. Women, suffering from antenatal anxiety and depression symptoms tend to take less good care of themselves (e.g. neglecting personal hygiene, the occurrence of sleeping problems, increased drinking and smoking habits, neglecting prenatal care), which may influence the development of the foetus.[24-27] Another indirect way in which antenatal anxiety and depression might influence the mental development of the offspring is when the antenatal psychopathology remains after delivery and turns into postnatal psychopathology. In this way, mother-child attachment might be endangered, because the mother has a reduced ability to respond to the child. Children from anxious and depressed mothers are breastfed for a shorter time[28] and have a higher risk of insecure attachment, which in turn is associated with cognitive, behavioural and emotional problems.[29-32] Finally, the association between antenatal psychopathology and adverse outcomes in the offspring might be indirect because this could be explained by a shared genetic or environmental predisposition between mother and child.

Whatever the actual mechanism(s) involved is/are, there is convincing evidence that children whose mothers suffered from anxiety or depression during pregnancy have an increased risk of behavioural, emotional and developmental problems.[14-20] Additionally, when these symptoms are present during the postpartum period, women express more negative emotions and are less sensitively attuned to their children.[33] This may have adverse effects on the child, e.g. attachment insecurity,[34-37] delay in emotional development[37] social and interaction difficulties,[38] and increased risk of developing violent behaviour.[39] Although maternal postpartum depression is associated with mental health problems in childhood, it is largely unknown to what extent this association could be explained by parental psychopathology outside the postpartum period. Furthermore, there is debate whether the association is specific to the internalising or externalising domain of psychopathology and whether the effects extend into adolescence.[37,40-44]

Whatever the case may be, at population level substantial total mental health gains may be accomplished when depressed or anxious women are adequately treated during their pregnancy, even if the effect size of the treatment is relatively small.

Early identification of risk factors

Parts of this thesis focus on risk factors for anxiety and depression during pregnancy. Identification of these risk factors may lead to identification of vulnerable groups of pregnant women, which eventually may lead to more effective targeting of prevention programmes and treatments. Risk factors include earlier (episodes of) psychopathology, unintended pregnancy, low social support, low socio-economic status (SES), and negative life events.[45-47] This thesis will focus on a number of potential risk factors, of which a short description follows. More detailed descriptions of these and other risk factors follow later at a later stage in this thesis.

Negative life events

A well-known general risk factor for depression is the experience of a negative life event.[46,47] Indeed, negative life events experienced before pregnancy have shown to be a strong predictor of depression during pregnancy and possibly also anxiety.[46,47]

However, the relevance of the timing of events is still unclear.[46-48] Earlier research among adults from the general population showed that the association between negative life events and psychopathology is generally stronger when the life event happened more recently.[49,50] A different pattern is observed for childhood traumas of which the effects show substantial latency, i.e. they strongly link to an increased risk of psychopathology in adulthood.[51,52] Whether these time relationships generalize to pregnancy is, however, still unknown.

Socio-economic status

In both general population and in postpartum women, low socio-economic status (SES) has been associated with depression and anxiety.[53,54] Because antenatal and postnatal psychopathology are strongly correlated,[55] low SES may also be a risk factor for antenatal anxiety and depression.[47,48] Yet, the literature is still inconclusive about which aspects of SES, paternal and maternal, play a role.[46] Low SES and negative life events before pregnancy are not only associated with anxiety and depression during pregnancy, but may also have an adverse effect on birth weight and preterm birth which underlines the importance of their study.[56-58]

As low SES and negative life events are likely to be interrelated and because women with a low SES may have less mental resources and may be less able to cope with negative life events earlier in life, it may well be that these risk factors interact. Therefore, it can be hypothesised that women with a low SES are more vulnerable to the effects of negative life events on anxiety,

depression, and low birth weight or preterm birth compared to their peers with a normal or high SES. To date this is uncertain.

Even less is known about the prevalence and severity of anxiety and depression among pregnant women in the developing country Nicaragua. Depression and anxiety rates among pregnant women are less well known, but presumably higher. Indeed, it has been estimated that in developing countries, one in three to one in five pregnant women experiences a significant mental health problem, comparing to one in ten in developed countries.[59] It is assumed that this high prevalence is the result of lower socio-economic development of the population, abuse, violence, and deficiency in mental health care.[59,60] Nevertheless, to date the prevalence of depression and anxiety during pregnancy and their comorbidity are not known for the Central America region.

Personality traits

One of the earlier mentioned adverse effects of anxiety and depression around pregnancy, is that women who experience these symptoms breastfeed for a shorter period of time and are less likely to exclusively breastfeed.[28,61,62] A recent study even showed that psychosocial factors are the strongest predictors of exclusive breastfeeding, i.e. receiving (expressed) breast milk only and, if necessary, drops and syrups like vitamins, minerals and medicines.[28,63] Nevertheless, a recent review concluded that there is very limited research examining roles of psychosocial factors on six months exclusive breastfeeding.[64]

A possibly important factor in relation to breastfeeding is personality, which can be described as individual differences in thoughts, feelings and behaviour. The well-known Five Factor Model, also known as 'Big Five', describes personality as consisting of five personality traits that describe individual differences between people.[65] Each trait can be further divided into six facets, as presented in table 1.

Table 1: Big Five personality traits and their facets

Agreeableness	**Conscientiousness**	**Extraversion**	**Neuroticism**	**Openness to experience**
Altruism	Achievement striving	Activity	Anger	Action
Compliance	Competence	Assertiveness	Anxiety	Aesthetics
Modesty	Deliberation	Excitement-seeking	Depression	Fantasy
Straight-forwardness	Dutifulness	Gregariousness	Impulsiveness	Feelings
Tender-mindedness	Order	Positive emotions	Self-consciousness	Ideas
Trust	Self-discipline	Warmth	Vulnerability	Values

Although studies assessing relationships between personality and breastfeeding lacked methodological robustness, these showed positive associations of higher levels of agreeableness, extraversion, and openness with breastfeeding.[66-68] Furthermore, in two recent large meta-analyses in general population, low consciousness, low extraversion, high neuroticism personality traits were associated with major depression and general anxiety disorder.[69,70] Two studies among pregnant women showed that low agreeableness, low consciousness, and high neuroticism seem to be associated with symptoms of depression.[71,72]

Because of these associations, breastfeeding outcomes may in part be explained by symptoms of anxiety or depression. However, this explanation has never been studied.

Current treatment options

Parts of this thesis focus on treatment of anxiety and depression during pregnancy. According to the current guidelines of the Dutch Association of Obstetrics & Gynaecology (Nederlandse Vereniging voor Obstetrie & Gynaecologie; NVOG),[73] the British National Institute for Health and Care Excellence (NICE),[74] the Australian Beyondblue,[75] the American Psychiatric Association (APA),[76] and the American College of Obstetricians and Gynecologists (ACOG),[76] three treatment options for ante- and postnatal anxiety and depression should be considered: medication, psychotherapy, or a combination of both.[73-76]

Due to ethical concerns, to date, no experimental research has been performed to proof the effects of anxiolytics and antidepressants during pregnancy. According to the guidelines, it is implausible that their effects with pregnant women differ from effects in the case of non-pregnant women. However, when using medicines as treatment, the advantages of decreasing the maternal symptoms should be equated to the disadvantages of the possible dose-dependent toxicity on the unborn foetus.[73-76] Although there is a lot of clinical experience in using tricyclic antidepressants (TCAs), both in non-pregnant and in pregnant women, prudence is called for because these can cause neonatal withdrawal reactions.[77] Monoamine-oxidase inhibitors (MAOIs) should be avoided during pregnancy because of the risk of a maternal hypertensive reaction.[78] Additionally, there are reports of teratogenicity while using MAOIs.[78] A commonly used group of antidepressants is formed by the serotonin-reuptake inhibitors (SSRIs). According to the guidelines, none of the types of SSRIs is clearly preferred during pregnancy, again due to absence of research.[73,74] Nevertheless, Sertraline (Zoloft®, Lustral®) and Citalopram (Cipramil®, Celexa®) may have the lowest risk of adverse neonatal effects.[73] Conversely, Paroxetine (Seroxat®, Paxil®) has been associated with low birth weight and congenital

abnormalities.[73,79] Finally, Escitalopram (Lexapro®, Cipralex®) and Fluvoxamine (Fevarin®, Luvox®) have been less researched.[73,79] When a woman uses SSRI's during pregnancy, both delivery in a hospital and neonatal observation under supervision of a paediatrician for a minimum of 12 hours after birth are recommended, because of the risk of neonatal persistent pulmonary hypertension.[73] As in every medicinal therapy, the lowest possible dosage, still providing an effective result, should be prescribed, in pregnant as well as in breastfeeding women.[73-76,78,79]

Likewise, the evidence of the effectivity of psychotherapy as treatment for psychopathology during pregnancy is insufficient.[80-82] Nevertheless, women seem to have a preference for cognitive behavioural therapy over antidepressants.[83] Cognitive behavioural therapy is one of the most often applied forms of psychotherapy and is based upon a combination of basic behavioural and cognitive principles.[84] In the non-pregnant population, cognitive behavioural therapy has proven to be effective in many randomised controlled trials and it is implausible that its effects in pregnant women differ from effects in non-pregnant women.[85,86] However, there is only mixed evidence of beneficial effects of cognitive behavioural therapy during pregnancy.

Literature provides only four randomised controlled trials that investigated the effect of cognitive behavioural therapy of antenatally provided cognitive behavioural therapy. Three studies assessed the effect of the therapy on anxiety or depressive symptoms during pregnancy. One showed a non-significant reduction in depression symptom level,[80] another showed a significant reduction in depression symptom level,[81] and only one assessed both depression and anxiety symptom levels. In the last study, no beneficial effects of cognitive behavioural therapy on symptom levels of anxiety or depression were shown.[82] None of the four trials investigated perinatal effects and only one assessed effects on the offspring. The latter study showed no effect of antenatal cognitive behavioural therapy on offspring cognitive, socio-emotional, or physical development at age 7. Nevertheless, this study only assessed parent-reported child development, which may have been subject to reporting bias, and no offspring behavioural problems were assessed.[87]

In conclusion, there is sparse evidence for the effectivity of cognitive behavioural therapy and adverse foetal effects cannot be precluded.[88] While perinatal outcomes such as birth weight and gestational age at birth depend on many factors, psychopathology as well as its treatment may negatively affect them.[73-76] Clearly, more evidence is needed to assess the effectiveness and possible perinatal 'side effects' of cognitive behavioural therapy during pregnancy.

In part II of this thesis, the effectiveness of a cognitive behavioural therapy intervention was investigated among pregnant women with subclinical

symptoms of anxiety and depression. The therapy was designed especially for pregnant women with these symptoms and consisted of several optional modules with specific evidence-based cognitive behavioural therapy interventions. These focused on the treatment of anxiety disorders, depressive disorders, trauma and post-traumatic stress disorder. In addition, this treatment was targeted at identifying and challenging dysfunctional cognitions, schemata (i.e. cognitive frameworks that help to organise and interpret information) and exploring with the patient alternative coping styles. More detailed descriptions of the intervention as well as the study design follow later on in this thesis.

Studies in this thesis

In this thesis, data was used from multiple cohorts. Dutch data was derived from TRAILS, the PAD-study and the PROMISES-study. One of the chapters presents a explorative study in Nicaragua, where a small population-based study was performed.

TRAILS

The TRacking Adolescents' Individual Lives Survey (TRAILS) is a prospective cohort study of Dutch (pre)adolescents, with the aim to chart and explain the development of mental health from preadolescence into adulthood, both at the level of psychopathology and the levels of underlying vulnerability and environmental risk. Sample selection of children around twelve years of age from the general population attending participating schools concerned five municipalities in the North of the Netherlands. A parallel clinical cohort included children who have been referred at least once to the child psychiatric outpatient clinic of the University Medical Center Groningen at any point in their life. Measurements and procedures in TRAILS-CC were identical to those in the general population cohort. In TRAILS, 2230 children were included in the general population cohort, as well as 543 children in the clinical cohort.

PAD-study

The Pregnancy Anxiety and Depression (PAD)-study is a population-based observational prospective cohort study wherein psychological, medical and social factors during pregnancy and the postpartum period were investigated. Women in their first trimester of pregnancy were invited to participate when visiting one of the 109 participating midwifery practices or nine participating gynaecology and obstetrics departments throughout the Netherlands, or through advertisements in nation-wide media. Only women not mastering the Dutch language were excluded. Before entering the study,

women provided written informed consent, which includes the option to give permission to the researchers to derive medical birth records. Participants were asked to complete online questionnaires at inclusion (around 10-15 weeks of gestation), at 24 and 36 weeks of gestation and at 6 and 24 weeks after pregnancy. In the PAD-study, 8143 women were included.

PROMISES-study

The Pregnancy Outcomes after a Maternity Intervention for Stressful EmotionS (PROMISES)-study is a randomised controlled single-blind trial that assesses the effects of cognitive behavioural therapy in 282 pregnant women, compared with care as usual. Participants of the PAD-study showing at least moderate symptoms of anxiety and/or depression were invited to participate in the PROMISES-study. Only women currently receiving psychotherapy, having a high suicidal risk, having a substantial physical disease, presenting with illegal substance abuse, or having a psychiatric disorder, psychoses or manic disorder, were excluded from participation in the PROMISES-study. In addition to the assessments of the PAD-study, the diagnostic SCID-I interview was administered, and participants were asked to complete online questionnaires at 12 and 18 months after pregnancy. Outcome measures included changes in the levels of anxiety and depressive symptoms of the women, perinatal outcomes as derived from medical birth records, and cognitive, fine and gross motoric development as well as child behaviour in the offspring as assessed at 18 months of age.

Nicaragua study

The Nicaragua study is a population-based cross-sectional study, which consisted of pregnant women who visited a public hospital or one of the two participating community health centres in the rural south of Nicaragua. During the inclusion period, all pregnant women were invited to participate in this study. When women were not able to read the questionnaire due to illiteracy, the researchers or nurses read the questionnaire aloud. We believed this was a better method then excluding all analphabetic women. The only women who were excluded from participation were women who had no oral mastery of the Spanish language. Before entering the study, women provided informed consent. Participants were asked to complete a questionnaire on symptoms of psychopathology and availability of professional psychological help. In the Nicaragua study, 98 women were included.

Detailed information about the design of and measurements within these studies are described further on in this thesis.

Outline and scope of this thesis

This thesis consists of two parts, of which the first consists of observational studies and the second of an intervention study. The observational studies are several analyses, based on the earlier mentioned TRAILS, PAD, and Nicaragua studies. The intervention study, PROMISES, is a randomised controlled trial designed to assess the effects of cognitive behavioural therapy during pregnancy on both mother and child, when compared to care as usual.

Part I: Observational studies

Chapter 2 describes the screening and treatment of two women with psychopathology during pregnancy. Although the patients experienced different complaints in different situations, the impact on woman, partner and child(ren) was in both cases tremendous. The cases make clear how relevant early screening and treatment of symptoms of anxiety and depression is during and after pregnancy.

Chapter 3 demonstrates the associations of the number of prior negative life events with symptoms of anxiety and depression early in pregnancy. Furthermore, we assessed which aspects of SES are associated with anxiety and depression. Finally, we investigated potential effect modification of the associations of the number of prior negative life events with symptoms of anxiety and depression by relevant aspects of SES. Additionally, we repeated these analyses on perinatal outcomes.

Chapter 4 presents our explorative study to investigate the prevalence and severity of anxiety and depression during pregnancy in the Central American developing country Nicaragua, as well as the availability of mental health care. We compared our Central-American findings to the findings of the PAD-study in the Netherlands.

Chapter 5 describes the possible independent associations of the big five personality traits and symptom levels of anxiety and depression with meeting the World Health Organisation (WHO)-recommendation of six months exclusive breastfeeding.

Chapter 6 demonstrates the associations of postpartum depression with internalising and externalising mental health problems in the offspring during adolescence. We investigated whether the associations were independent of parental lifetime psychopathology, to gain insight into a potential direct effect of postpartum depression.

Part II: Randomised controlled trial

Chapter 7 presents the design of the PROMISES-study. This chapter is based on the published protocol and a book chapter. Additionally, the screening of participants in the PAD-study for eligibility for participation in the PROMISES-study is described.

Chapter 8 reports the effects of cognitive behavioural therapy on the level of anxiety and depressive symptoms at 36 weeks of gestation, as compared to care as usual. We assumed additional reduction in symptom levels in participants who received cognitive behavioural therapy than in participants who received care as usual.

Chapter 9 describes the effects of cognitive behavioural therapy on perinatal outcomes including birth weight and gestational age at birth, as compared to care as usual. We hypothesised that perinatal outcomes were better in participants who received cognitive behavioural therapy than in participants who received care as usual.

Chapter 10 is a preliminary report on the effects of cognitive behavioural therapy on child outcomes at 18 months, as compared to care as usual. We assessed cognitive, fine and gross motoric development as well as child behaviour, as a predictor for psychological problems later in life. We assumed that both child development and child behaviour were more optimal in offspring of participants who received cognitive behavioural therapy than in offspring of participants who received care as usual.

Chapter 11 provides the general discussion of the thesis and gives recommendations for clinical practice and for future research.

The thesis ends with a summary in English as well as in Dutch.

PART I

Observational studies

CHAPTER 2

Is she on cloud nine, or are black clouds gathering over her? Psychopathology during and after pregnancy

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Abstract

This article describes two patients with psychosocial problems during and after pregnancy. The first woman suffers from an obsessive-compulsive disorder and developed a postpartum depression after her first pregnancy. Her second pregnancy was marked by uncertainty, anxiety, and stress. Her caregivers noticed her problems and referred her to a Psychiatry-Obstetrics-Paediatrics (POP)-team, which provided her with a successful treatment. The second woman had physical symptoms, which were largely ascribed to an antenatal depression and were effectively treated using antidepressants and cognitive behavioural therapy. Although these patients experienced different problems in different situations, the impact on the woman, partner and child(ren) was tremendous in both cases.

This article makes clear that early screening and treatment of symptoms of anxiety and depression are important during and after pregnancy. Vigilance and screening by midwives, general practitioners, and obstetricians may help in early recognition and ultimately in earlier treatment, either medicinal and/or using psychotherapy, which may reduce or even prevent harmful consequences.

Background

The time around a pregnancy is accompanied by many emotions. Mostly, the main emotion is happiness, as a result of the hope of an uncomplicated pregnancy, a pleasant postpartum period and a healthy child. However, many pregnant women suffer from symptoms of anxiety and depression. Nevertheless, recognition and treatment are still insufficiently integrated in obstetric care. This article intents to show that screening and timely referral to specialized care are important because of the tremendous impact of the complaints on women, partners, and child(ren).

Case descriptions

Patient A, a 25 years old woman, gravida 2 para 1, was referred to the POP-team, consisting of a psychiatrist, an obstetrician, and a paediatrician, in the first trimester of her second pregnancy, because of mental health problems. Since her childhood, she suffered from an obsessive-compulsive disorder (OCD), but she refused treatment. In addition to anxiety and depression disorders, OCD was present in her religious family.

During her first pregnancy, no attention was paid to her OCD. During her maternity time, she developed a postpartum depression with psychotic features. She experienced delusions and thought that her child had a deformed and frightening appearance, which was objectively incorrect. In the course of time, her gloominess and delusions disappeared and therefore she still felt no need for treatment.

In the following two years, the OCD symptoms returned: she had cleaning compulsions and obsessional thoughts about her son, soiling himself. As a consequence of these thoughts, she restricted his freedom of movement and prohibited him playing outside or crawling on the floor, which ultimately resulted in a lot of conflicts with her husband.

The results of a screening in the first antenatal consult during her second pregnancy indicated mental problems, whereupon the midwife referred the woman to the POP-team. During the intake appointment, the psychiatrist saw a young woman with a well-groomed appearance, who was friendly in contact. She was openhearted about her medical history and had an adequate insight and understanding of her progressing symptoms of OCD. During the intake, she made normal eye contact, she reacted properly and adequate, her attention was easy to attract and she could focus well. Her memory was intact, her cognition appeared to be normal, and she was well oriented in time, place, and person. Her perceptions were normal and she told the psychiatrist that she had no delusions or hallucinations after the postpartum period of her first pregnancy. Since her second pregnancy, she

had more obsessive and anxious thoughts. Nevertheless, her mood was normal and she had no suicidal thoughts.

Because the woman noticed that her symptoms were increasing, she accepted treatment, in contrast to the years before. The POP-team offered her a cognitive behavioural therapy (CBT), which was provided during the remaining months of her pregnancy. During these therapy sessions, anxiety and obsessional thoughts were the main subjects. In addition, attention was paid to the prevention of a depression. The CBT was, after a careful explanation of the advantages and disadvantages, medicinally supported using a serotonin reuptake inhibitor (SSRI) named Sertraline (Zoloft®, Lustral®) 50 milligrams daily. Sertraline has a therapeutic function in OCD patients and works preventative on averting a postpartum depression.

In the following months, the POP-team kept in close touch with the patient. Her psychiatric symptom levels decreased and there was no need to increase the dose of her Sertraline. She reported to be less anxious and had less obsessive-compulsive thoughts and behaviours aimed at herself, her partner and child.

After an uncomplicated pregnancy of 38 weeks, she gave birth to a healthy boy. His birth weight was below average (2900 grams; -1 standard deviation; SD) and he had a weak start (Apgar scores of 2, 6, and 8, after 1, 5, and 10 minutes). However, his umbilical artery pH was normal. He recovered quickly and his mother was very proud. To everyone's satisfaction the woman's postpartum period went by uneventful. The following months her psychiatric situation remained stable and she finished her therapy. She continued the use of Sertraline because of the effect on the OCD.

Patient B, a 24 years old woman, gravida 1 para 0, was referred to the POP-team because of mental health complaints, at the end of the second trimester of her pregnancy. The patient grew up in a family with a low socio-economic status (SES). She was poorly educated, was unemployed and suffered from a strong fear of performance over the years. In addition, she had lost her little brother when she was young.

In the years before her pregnancy, she tried to get pregnant from her former partner, but despite fertility examinations and several tests these attempts remained unsuccessful. The tension and uncertainty resulting from the unfulfilled desire to have a child resulted in a lot of stress and eventually in the end of the relationship. Only two months after the start of her new relationship, the patient was pregnant by her new partner. He insisted on an abortion, but she refused and ended this relationship.

During an antenatal consult with her midwife, the patient told that she was often nauseated and vomited frequently. Besides that, she was very tired,

melancholic, and had been fretting for weeks. The joy of being pregnant decreased and ultimately she considered offering her child for adoption. At the end of the second trimester of her pregnancy, her general practitioner referred her to the POP-team.

During the intake appointment, the psychiatrist saw a young woman with a moderately groomed appearance, who looked very exhausted. While she was friendly and cooperative, she made a passive and submissive appearance. She had an inadequate insight in her condition: she saw no association between her somatic and psychiatric symptoms. Her attention was easy to attract and she could focus well. Her memory was intact, her cognition appeared to be normal, and she was well oriented in time, place, and person. Her perceptions were normal and she told that she had no delusions or hallucinations. She had a negative thought about her self-image and her future. Her mood was dejected and depressed and her affect was flat, but she had no suicidal thoughts. The psychiatrist diagnosed her with an antenatal depression. In her family medical history, no depression was present.

After a careful explanation about the psychiatric origin of her somatic complaints, patient was willing to be treated with CBT and medication. Because she did not tolerate Sertraline, the POP-team decided to prescribe another SSRI, named Citalopram (Cipramil®, Celexa®) 10 milligrams daily. In the following months, she was fretting less and her mood improved. Her nausea disappeared, she slept better at night, and was less tired during the day.

After an uncomplicated pregnancy of 38 weeks, she gave birth to a healthy boy. His birth weight was below average (2840 grams; -1 SD) but he had a good start (Apgar scores of 9, 10, and 10, after 1, 5, and 10 minutes). The pH of the umbilical artery was normal. The patient was very proud of her son and her postpartum period went by without both physical and mental problems. She told that she had benefited a lot from the CBT. After finishing the treatment of the POP-team, she continued her medication because of the positive effect on de prevention of postpartum depression. After six months, she reduced and eventually stopped the Citalopram, under the supervision of her general practitioner.

Discussion

Psychiatric problems are highly frequent complications of pregnancy. Of all pregnant women, 10-20% suffers from symptoms of anxiety and depression.[1,2] Besides on the pregnant women, these symptoms have adverse effects on perinatal outcomes and the unborn children.[17] Thus, recognition and timely treatment of psychiatric complaints in pregnant women are important for the mothers to be, their partners, and children.

In spite of the nature and frequency of psychiatric problems, systematic screening is not integrated in obstetric care. Midwives and obstetricians do assess psychiatric disorders in the medical history of the patient, but they often do not screen on risk factors and symptoms of psychiatric disorders.[8,9] During her first pregnancy, patient A was not screened on psychiatric disorders in her medical history, or her midwife did not realise the consequences of a positive screening result. During her second pregnancy, her increased risk was recognised and resulted in an effective referral by the general practitioner to the POP-team.

Risk factors

Literature shows that an earlier episode of psychopathology is not the only risk factor for anxiety and depression during or after pregnancy. Other risk factors include an unintended pregnancy, low social support, low SES, and negative life events, especially child traumas and events that happen shortly before the pregnancy.[45,46] Besides, the experience of symptoms of anxiety or depression during pregnancy is known to be a strong predictor of such symptoms in the postpartum period.[55]

In the joint guideline of the Dutch Association of Obstetrics & Gynaecology (Nederlandse Vereniging voor Obstetrie & Gynaecologie; NVOG), the Dutch Association of Paediatrics (Nederlandse Vereniging voor Kinder-geneeskunde; NVK), and the Dutch Association of Psychiatry (Nederlandse Vereniging voor Psychiatrie; NVvP), it is advised to systematically screen on these risk factors.[73] Aside from the midwife or obstetrician, the general practitioner can indicate a patient with an increased risk and enable a quick referral to a POP-team for further diagnostics and treatment.
Patient B had an increased risk of anxiety and depression, based on her poor social network, low SES, the loss of her brother (a major childhood negative life event), and the stress she experienced before and during pregnancy.

Differential diagnosis

Anxiety and depression are not the only mental health problems pregnant women might suffer from. Psychiatric problems that may occur outside of

pregnancy, for example schizophrenia, autism spectrum disorders, and eating disorders, may as well occur during pregnancy. Particularly bipolar disorders should be kept in mind, because these are associated with postpartum psychoses.[90] Furthermore, alcohol and drug use should be detected because of the major adverse consequences for the unborn child.[91] As alternative diagnoses, hypo- and hyperthyroidism should be considered, as well as physiological (emotional) manifestations of the physical and social changes during pregnancy.

Treatment

Above-mentioned multidisciplinary guideline advises to treat psychiatric disorders during pregnancy on time.[73] In patients with anxiety and/or depression, three treatment options are available, i.e. antidepressants, psychotherapy, or a combination of both.

Due to ethical concerns on performing research on pregnant women, both beneficial and possible adverse (side) effects of these treatment options have not been well studied, but it is unlikely that the effectivity differs between pregnant versus non-pregnant women. When medicinal treatment is chosen, therapeutical benefits should be weighted up to the possible dose-dependent toxicity for the unborn child.[73]

Although there is a lot of clinical experience in using tricyclic antidepressants (TCAs), prudence is called for because these can cause neonatal withdrawal reactions.[78] Monoamine-oxidase inhibitors (MAOIs) should be avoided during pregnancy because of the risk of a maternal hypertensive reaction and because there are reports of teratogenicity while using MAOIs.[78]

A commonly used group of antidepressants is formed by the SSRIs. According to the guidelines, none of the types of SSRIs is clearly preferred.[73] However, the SSRIs that were used in the treatment of patients A and B, namely Sertraline and Citalopram, probably have the smallest risk of adverse neonatal effects.[73] Escitalopram (Lexapro®, Cipralex®) and Fluvoxamine (Fevarin®, Luvox®) have been less researched. Paroxetine (Seroxat®, Paxil®) has been associated with low birth weight and congenital abnormalities.[73] Because of the risk of neonatal persistent pulmonary hypertension, delivery in a hospital, as well as neonatal observation under supervision of a paediatrician for a minimum of 12 hours after birth are recommended when a woman uses SSRIs during pregnancy. Like in every medicinal therapy, the lowest possible dosage, still providing an effective result, should be prescribed, both in pregnant and in breastfeeding women.[73]

Likewise, the evidence of the effectivity of psychotherapy as a treatment for psychopathology during pregnancy is insufficient. Cognitive behavioural therapy is one of the most often applied forms of psychotherapy and is based

upon a combination of basic behavioural and cognitive principles. In the non-pregnant population, cognitive behavioural therapy has proven to be effective and it is implausible that its effects in pregnant women differ from effects in non-pregnant women. However, there is only mixed evidence of beneficial effects of cognitive behavioural therapy during pregnancy. Furthermore, risks for the unborn child have not yet been studied.[92]

Both patient A and B benefited from the combination of CBT and an SSRI. In non-pregnant women this combination is very effective in reducing symptoms of psychopathology.[92] However, effects on the foetal are still unknown. The children of both patients were born at term but had low birth weights and the child of patient A had a weak start. While perinatal outcomes result from many factors, these outcomes may be adversely influenced by the psychopathology, or by the treatment.[73] Therefore, the expertise of the POP-team is helpful in balancing the pros and cons of the treatment options.

In more and more Dutch hospitals, care for pregnant women with psychiatric complaints is organised in POP-teams. These multidisciplinary teams are desirable in the individual assessment of cases. To increase the success rate of the treatment, close cooperation with the general practitioners and their psychiatric nurse practitioners is recommended. They know the context and family situation of their patients therefore the can provide a quick adequate screen and referral. Involvement of the paediatrician in the POP-team is meaningful in the anticipation of the effects on the child, antenatally and postpartum.

Conclusion

These cases indicate that awareness and early screening of symptoms of anxiety and depression is of great importance during and after pregnancy. While patients A and B had divergent symptoms in different situations, the complaints had a tremendous impact in both cases. Timely observation and adequate treatment have reduced or even prevented adverse consequences. It is important to evaluate the risk of psychiatric problems and quickly refer pregnant women to a POP team. Treatment, consisting of medicines and/or psychotherapy may be started earlier to reduce adverse consequences. The multidisciplinary approach of the POP-team is preferred in the diagnostics, treatment, and follow-up of this complex group of patients.

CHAPTER 3

Low SES increases effect of negative life events on antenatal psychopathology during pregnancy: a population-based cohort study

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Abstract

Background

Prevention of psychopathology during pregnancy may be favourable for mother and child. Both low socioeconomic status (SES) and negative life events are documented risk factors for antenatal anxiety and depression, preterm birth and birth weight. This study aimed to assess whether the adverse effects of negative life events increase with lower SES and which aspects of SES are most relevant.

Methods

Data was derived from a population-based cohort study in the Netherlands including 5,398 women in their first trimester of pregnancy. The number of negative life events prior to pregnancy, aspects of paternal and maternal SES and symptoms of anxiety and depression were assessed. Associations of the number of negative life events with anxiety, depression, birth weight and gestational age were quantified.

Results

The number of negative life events, particularly when they had occurred recently and maternal aspects of low SES (educational level, unemployment and income) were associated with increased symptoms of anxiety and depression (Z-score per life event ranged for anxiety 0.022–0.034, $p<0.001$ and for depression 0.057–0.084, $p<0.001$). Furthermore, low SES increased the adverse effects of negative life events ($p<0.01$ for interaction). Obstetric outcomes showed similar trends, although mostly not statistically significant.

Conclusions

Low SES increases the adverse impact of negative life events on anxiety and depressive symptoms in pregnancy and possibly also on birth weight and gestational age. Interventions for anxiety and depression during pregnancy should be targeted particularly to unemployed, less-educated or low-income women who recently experienced negative life events.

Background

Symptoms of anxiety and depression are highly frequent complications of pregnancy: 10-15% of all pregnant women experience symptoms of anxiety and/or depression.[1,2] Undergoing these symptoms during pregnancy is a major risk factor for preterm birth, low birth weight,[12,13] and postpartum psychopathology,[47,93] which in turn is associated with poor child outcomes, including insecure mother-child attachment,[32] and ultimately emotional, cognitive and behavioural problems in childhood and adolescence.[14-20]

Therefore, to target and design interventions it is essential to have a clear understanding of the determinants of depression and anxiety during pregnancy. A well-known general risk factor for depression is the experience of a negative life event.[46,47] Indeed, negative life events experienced before pregnancy have shown to be a strong predictor of depression during pregnancy and possibly also anxiety.[46-48]

However, the relevance of the timing of events is still unclear.[46-48] Earlier research among adults from the general population showed that the association between negative life events and psychopathology is generally stronger when the life event happened more recently.[49,50] A different pattern is observed for childhood traumas of which the effects show substantial latency, i.e. they strongly link to an increased risk of psychopathology in adulthood.[51,52] Whether these time relationships generalize to pregnancy is however unknown.

Not only negative life events, but also low socioeconomic status (SES) has been associated with depression and anxiety. The latter has been shown in both general population as well as in postpartum women.[53,54] Therefore, low SES may as well be a risk factor for antenatal anxiety and depression.[47,48] Yet, the literature is still inconclusive about which aspects of SES, maternal and paternal, play a role.[46] Low SES and negative life events before pregnancy are not only associated with anxiety and depression during pregnancy, but may also have an adverse effect on birth weight and preterm birth which underscores the importance of their study.[56-58]

As low SES and negative life events are likely to be interrelated and because women with low SES may have less mental resources and may be less able to cope with negative life events earlier in life it may well be that these risk factors interact. Therefore, it can be hypothesized that low SES women are more vulnerable to the effects of negative life events on anxiety, depression, and low birth weight or preterm birth compared to their peers with normal or high SES. To date this is unknown.

To our knowledge, the present study is the first to investigate the associations of negative life events in different periods in life and aspects of low SES with symptoms of antenatal anxiety and depression as well as low birth weight or prematurity and their potential interaction.

Methods

Study population

This study was carried out using the baseline measurements of the Pregnancy, Anxiety and Depression (PAD) study.[94] This population-based prospective cohort study was designed to investigate symptoms of and risk factors for antenatal and postnatal anxiety and depression. All pregnant women in their first trimester of pregnancy visiting a total of 109 collaborating primary obstetric care centres and 9 hospitals in the Netherlands were invited to participate by their midwife or gynaecologist. Due to logistical reasons it has been impossible to determine how many women actually have been invited and consequently to determine the exact participation rate. Because the number of participating women was lower than expected we conducted a survey among participating midwives and gynaecologists. The results indicated that the vast majority of them were unable to hand out the forms to all visiting women due to time constraints and that they had not specifically invited women they suspected to have risk factors, psychopathology or other conditions. Therefore, we have no reason to believe that responders and non-responders differed in any considerable way with respect to characteristics relevant to the present study.[94]

Written informed consent was obtained. After the baseline questionnaires at the end of the first trimester, follow-up assessments took place at the end of the second and third trimesters, as well as six weeks and three and six months postpartum. Data was collected from May 2010 to November 2014. By the end of that period, 5,398 women had completed baseline assessments.

The PAD-study was approved by the medical ethical review board of the University Medical Center Groningen.

Measurements

The Spielberger State Trait Anxiety Inventory (STAI) was used to assess the level of anxiety.[95] We used the 6-item short-form to measure state anxiety which produces scores similar to those obtained using the full-form.[95] The 10-item Edinburgh Postnatal Depression Scale (EPDS) was used to measure depression symptom levels.[96] This version of the EPDS has shown to be valid during pregnancy.[97]

The Negative Life Events Questionnaire (NLEQ) was used to assess adverse life events prior to pregnancy.[98] The mentioned life events were: divorce (parent, self or child), new relationship, moving, long-term and/or severe illness (parent, sibling, partner, self, child or another important person (e.g. friend, in-laws, confidential advisor)), death (parent, sibling, partner, child or another important person), severe psychiatric problems (parent, sibling,

partner, child, self or another important person), suicide attempt (parent, sibling, partner, child, self or another important person), family violence, alcohol/drug abuse within family or relationship, being victim of a crime, victim of a severe accident, victim of sexual abuse, victim of assault, having an unwanted pregnancy. We distinguished different periods in life: (1) from birth until the age of 16 (childhood trauma); (2) from the age of 16 until two years before pregnancy (mean duration: 12.5 years, SD=4.4); (3) the two years before pregnancy.

SES was measured using a questionnaire based on the Leidsche Rijn study.[99] Five aspects of SES were documented: educational level (self and partner), occupation (self and partner) and their annual gross family income. Educational level was defined as the highest completed education, divided into three categories; low (elementary and lower tracts of secondary education), intermediate (higher tracts of secondary education and intermediate vocational education), and high (higher vocational education and university). Family annual gross income was divided into low (€0 – €30,999), modal (€31,000 – €59,999), and high (€60,000 or more).

All questionnaires were administered online.

Obstetric outcomes were obtained for a part of the study population. While we requested all midwives and gynaecologists in our study to provide birth records including data on birth weight and gestational age of participating women, this request was complied with for only 2867 (53.1%) women.

Multiple imputation and statistics

To avoid risk of bias and loss of statistical power in complete case analyses, missing data was imputed. We used multiple imputation by chained equations under the assumption that data was missing at random (MAR) or completely at random (MCAR).[100] Twenty datasets were imputed and combined according to Rubin's rules.[101] The percentage of missing data was approximately 22 (range: 15%; number of life events – 38%; family annual gross income). The missing data mechanism was studied for each of the variables, by predicting missingness of each of these variables from the other variables in the imputation model using multivariable logistic regression analyses. These analyses showed explained variances ranging from 0.6% to 27.1% (Nagelkerke's R^2), implying that data were at least partly missing at random, and consequently, multiple imputation may have minimized bias. The final imputation model included those variables that predicted the value of the incomplete variable and whether the incomplete variable was missing or not. Because the MAR nor the MCAR assumption can be proved we added complete case analyses as a sensitivity analysis. Because obstetric outcomes were only available in 53.1%, we did not impute birth weight and gestational age to the total population but rather performed complete case analyses.

We calculated descriptive statistics for maternal age, STAI- and EPDS-scores including the number of women who scored at least moderate symptom levels of anxiety (STAI-score >42) or depression (EPDS-score ≥12), the numbers of negative life events periods in life, aspects of SES, and obstetric outcomes. Measurements of symptoms of anxiety and depression exhibiting skewed distributions were transformed using the natural logarithms, before further analyses were conducted to satisfy the prerequisite assumptions of normality. To allow for valid comparison of effect sizes between the associations with anxiety, depression, birth weight, and gestational age we created Z-scores for the corresponding variables.

Using multivariable linear regression we assessed which aspects of SES were associated with levels of anxiety or depression. To facilitate comparison of effects of high numbers of life events with low SES, we inverted the SES scores: high scores represent low SES and vice versa. Statistically significantly associated aspects of SES were equally weighted combined into an aggregated variable, which was used in following analyses. To correct for shared variance between anxiety and depression, we adjusted the analyses of anxiety for depression, and vice versa. Subsequently, we repeated these analyses for birth weight and gestational age.

Hereafter, using multivariable linear regression we assessed associations of anxiety and depression as dependent variables with the number of negative life events categorized by period in life as independent variables. Furthermore, we researched which of the associations between number of life events and both anxiety and depression were modified by SES. This was done by adding an interaction term SES*number of life events as an independent variable and testing its statistical significance.

Additionally, we quantified the associations for the available obstetric outcomes (birth weight, gestational age, and birth weight corrected for gestational age by adding birth weight as independent variable). We repeated earlier analyses to assess the associations between the number of negative life events, categorized by period in life with obstetric outcomes, and which of these associations were modified by SES.

Multiple imputation and analyses were performed with SPSS 22 (IBM, USA). The level of statistical significance was conventionally set at 0.05, two-sided.

Results

Descriptive statistics

Characteristics of the study participants are presented in table 1. Most women and their partners were intermediate or highly educated, were employed, and had a modal family income. Of the 5,398 women, 693 (12.8%) had a STAI-score >42 and 311 women (5.8%) had an EPDS-score ≥12, indicating at least moderate symptom levels.

Table 1: Characteristics of the study participants (n=5,398)

Age, mean years (SD)	30.5 (4.4)
STAI-score, median (IQR)	33.3 (10.0)
EPDS-score, median (IQR)	4.0 (4.0)
Number of negative life events, median (range); N (%) >1	
- Age 0 – 16 years	1 (0 – 12); 1,525 (28.3)
- Age 16 – two years before pregnancy	2 (0 – 15); 3,671 (68.0)
- Last two years before pregnancy	1 (0 – 11); 1,646 (30.5)
Education, self N (%); **partner** N (%)	
- Low	220 (4.1); 528 (9.8)
- Intermediate	1,886 (34.9); 2,272 (42.1)
- High	3,292 (61.0); 2,598 (48.1)
Employed, self N (%), **partner** N (%)	4,844 (89.8); 5,221 (96.7)
Family annual gross income, N (%)	
- Low (€ 0 – € 30.999)	873 (16.2)
- Modal (€ 31.000 – € 59.999)	2,593 (48.0)
- High (€ 60.000 or more)	1,932 (35.8)
Birth outcomes, *N = 2,687*	
Birth weight, mean grams (SD)	3479 (602)
Gestational age, mean weeks (SD)	39.3 (3.0)

SD – Standard deviation, STAI – Spielberger State Trait Anxiety Inventory (min-max 20-80), EPDS – Edinburgh Postnatal Depression Scale (min-max 0-30), IQR – interquartile range.

Associations of aspects of SES with anxiety, depression, and birth outcomes

Significant associations were found between educational level of the woman (B 0.088 [95%CI 0.013, 0.162] p=0.021), employment status of the woman (B 0.205, 95%CI 0.146 – 0.264, p< 0.001), and family income (B 0.107 [95%CI 0.040, 0.174], p=0.002) with symptoms of anxiety. Except for educational level (B 0.010 [95%CI -0.070, 0.089], p=0.806), comparable associations were seen with symptoms of depression (employment status of the woman: B 0.210 [95%CI 0.151, 0.269], p< 0.001, family income: B 0.134 [95%CI 0.073, 0.195], p<0.001). Neither partners' educational level nor his employment status was associated with maternal anxiety or depression. Equal trends were observed for the adverse effects of aspects of low SES on birth weight and gestational age. However, none of these results were statistically significant (p=0.101 – 832).

Associations of aspects of negative life events with anxiety and depression, and effect modification by SES

As presented in table 2, the number of negative life events was almost equally associated with anxiety and depression. Strongest associations were observed for events that had happened in the two years before pregnancy, which were twice as strong as between age 16 and two years before pregnancy.

Furthermore, these associations were statistically significantly modified by SES, i.e. became larger with lower levels of SES. This regarded both anxiety as depression, except for the events that occurred between birth and the age of 16 years. Size of the effect modification by SES increased with time: adverse effects of negative life events which happened in the last two years before pregnancy were more strongly modified by SES than those which happened earlier in life.

Associations of negative life events with obstetric outcomes

Results of the multivariable linear regression analyses to assess the adverse effects of negative life events on obstetric outcomes are presented in table 3. Although the majority of the associations and effect modifications were not statistically significant (p=0.034 – 0.854), the observed trends were equal to the associations with symptoms of anxiety and depression, i.e. life events were associated with lower birth weight and lower gestational age. The strongest associations and effect modifications were observed for events that had happened in the two years before pregnancy, followed by childhood traumas (age 0 – 16 years) and negative life events that occurred between 16 years age and two years before pregnancy.

Correction for shared variance (between anxiety and depression, and between birth weight and gestational age) did not considerably affect the results. Results of complete case analyses were not notably different from imputed data analyses.

Table 2: Associations of number of life events per life period with anxiety and depression during pregnancy and effect modification by SES (*N=5,398)*

Number of negative life events per life period	**Associations with anxiety (STAI)**				**Associations with depression (EPDS)**			
			Effect modification				Effect modification	
	B (95% CI)	p-value	B (95% CI)	p-value	B (95% CI)	p-value	B (95% CI)	p-value
No. of life events (age 0 – 16 years)	0.027 (0.059 – 0.096)	< 0.001	0.067 (0.046 – 0.087)		0.069 (0.056 – 0.082)	< 0.001	0.119 (0.063 – 0.175)	
SES score	0.090 (0.070 – 0.110)	< 0.001	0.064 (0.040 – 0.088)		0.219 (0.165 – 0.273)	< 0.001	0.186 (0.117 – 0.255)	
Life events * SES			0.017 (0.009 – 0.026)	< 0.001			0.022 (-0.002 – 0.045)	0.074
No. of life events (age 16 – two years before pregnancy)	0.022 (0.018 – 0.025)	< 0.001	0.052 (0.035 – 0.069)		0.057 (0.047 – 0.066)	< 0.001	0.127 (0.082 – 0.172)	
SES score								
Life events * SES	0.106 (0.087 – 0.125)	< 0.001	0.070 (0.043 – 0.096)		0.260 (0.207 – 0.313)	< 0.001	0.177 (0.102 – 0.251)	
			0.013 (0.006 – 0.019)	< 0.001			0.029 (0.011 – 0.047)	< 0.001
No. of life events (last two years before pregnancy)	0.034 (0.029 – 0.040)	< 0.001	0.094 (0.065 – 0.122)		0.084 (0.069 – 0.100)	< 0.001	0.195 (0.119 – 0.270)	
SES score	0.096 (0.076 – 0.116)	< 0.001	0.062 (0.034 – 0.090)		0.236 (0.181 – 0.291)	< 0.001	0.173 (0.098 – 0.247)	
Life events * SES			0.025 (0.013 – 0.036)	< 0.001			0.046 (0.015 – 0.076)	< 0.001

Multivariable linear regression analyses. Symptoms of anxiety and depression were assessed using STAI- and EPDS-questionnaires and were subsequently standardized by calculating Z-scores. Educational level and employment status of the woman and family income were equally weighted combined to the variable SES score. SES scores were inverted: a high score represents a low SES and vice versa. CI – Confidence interval, EPDS – Edinburgh Postnatal Depression Scale, SES – Socioeconomic status, STAI – Spielberger State Trait Anxiety Inventory.

Table 3: Associations of number of life events per life period with obstetric outcomes and effect modification by SES (*N=2,687)*

Number of negative life events per life period	**Associations with birth weight (grams)**				**Associations with gestational age (weeks)**			
			Effect modification				Effect modification	
	B (95% CI)	p-value	B (95% CI)	p-value	B (95% CI)	p-value	B (95% CI)	p-value
No. of life events (age 0 – 16 years)	-0.024 (-0.049 – 0.002)	0.070	-0.129 (-0.244 – -0.015)		-0.002 (-0.027 – 0.022)	0.844	-0.050 (-0.161 – 0.062)	
SES score	-0.71 (-0.170 – 0.027)	0.155	-0.004 (-0.130 – 0.121)		-0.029 (-0.139 – 0.081)	0.604	0.001 (-0.142 – 0.144)	
Life events * SES			-0.046 (-0.095 – 0.003)	0.064			-0.021 (-0.068 – 0.026)	0.391
No. of life events (age 16 – two years before pregnancy)	-0.010 (-0.023 – 0.020)	0.330	-0.053 (-0.156 – 0.050)		-0.003 (-0.021 – 0.015)	0.732	0.005 (-0.093 – 0.103)	
SES score	-0.087 (-0.185 – 0.011)	0.080	-0.036 (-0.194 – 0.121)		-0.030 (-0.138 – 0.078)	0.579	-0.040 (-0.197 – 0.117)	
Life events * SES			-0.018 (-0.060 – 0.024)	0.405			0.003 (-0.036 – 0.043)	0.867
No. of life events (last two years before pregnancy)	-0.035 (-0.067 – 0.003)	0.034	-0.211 (-0.380 – -0.41)		0.003 (-0.027 – 0.033)	0.854	-0.138 (-0.290 – 0.015)	
SES score	-0.075 (-0.173 – 0.024)	0.139	0.027 (-0.106 – 0.161)		-0.032 (-0.142 – 0.078)	0.567	0.049 (-0.104 – 0.203)	
Life events * SES			-0.073 (-0.143 – -0.003)	0.040			-0.058 (-0.120 – 0.003)	0.062

Multivariable linear regression analyses. Birth weight and gestational age were standardized by calculating Z-scores. Educational level and employment status of the woman and family income were equally weighted combined to the variable SES score. SES scores were inverted: a high score represents a low SES and vice versa. CI – Confidence interval, SES – Socioeconomic status

Discussion

Main findings

In this large population based study we demonstrated that the number of prior negative life events was associated with symptoms of anxiety and depression early in pregnancy. These associations increase when the events happened more recently, except for childhood traumas. Furthermore, we found that aspects of SES: low maternal educational level, maternal unemployment, and low family income are not only directly associated with anxiety and depression, but also increase the adverse effects of negative life events. Additional analyses on obstetric outcomes showed comparable trends, although mostly not statistically significant.

Strengths and limitations

Findings of this study should be interpreted in view of some limitations. First, life events were documented using self-report checklists, which may have been prone to recall bias through its potential link with symptoms at the time of the assessments. Furthermore, each participant may have had a different length interval in which to experience a life event depending upon her age at time of pregnancy. This influences the duration of the middle category (age 16 to two years prior to pregnancy). However, the observed SD was relatively small, indicating a low dispersion. Second, we encountered a large amount of missing data. Although this is not uncommon in research using questionnaires among pregnant women, this should be mentioned as a limitation. Nevertheless, we studied missing data mechanisms, used multiple imputation, and performed complete case analyses as sensitivity analysis to reduce bias. Finally, measurements of symptoms of anxiety and depression were based on self-report questionnaires. No diagnosis could be made using these questionnaires, although both STAI and EPDS questionnaires are commonly used in identifying symptoms of psychopathology.[95-97]

On the other hand, a major asset of this study is the inclusion of a large population based prospective sample, which enhanced the study's precision and generalizability. The inclusion of women living in a large part of the Netherlands, in both rural and urban areas, further adds to the generalizability of our results. Implication of these findings may be that more attention should be paid to the assessments of both negative life events and SES in designing and implementing psychosocial interventions for pregnant women. Aspects of SES that are particularly relevant are low maternal educational level, maternal unemployment, and low family income. Interventions are likely most cost-effective when targeted at low SES women with a history of multiple life events, in particular those who have experienced recent events. Ultimately, preventing or reducing

psychopathology during pregnancy may prevent emotional, cognitive and behavioural problems in the offspring.[14-20]

Interpretation

Our finding that prior negative life events are associated with antenatal depression is consistent with present literature.[46,47] As we hypothesized, anxiety is equally associated as depression. Furthermore, we demonstrated that these associations are stronger when the event happened more recently, except for childhood traumas; this is consistent with literature about these associations among non-pregnant women.[49,50] However, subjective impact of the events was not assessed, so differences in associations may not be completely explained by temporality. Indeed, a life event during childhood may have greater emotional impact than when a comparable event happened during adulthood.

The associations of low SES with antenatal depression and anxiety have been shown earlier,[47,48] although literature was conflicting about which aspects of SES play a role. Lancaster et al found inconsistent results for low educational level, unemployment and low income with antenatal depression in their multivariable meta-analysis.[46] In our sample, we saw strong and significant associations for maternal unemployment and low family income with both anxiety and depression and additionally low maternal educational level with anxiety. Remarkably we did not see any association for educational level and employment status of the partner. Although maternal and paternal anxiety and depression frequently correlate ,[102] we did not find any literature on the association of paternal educational level and employment status on maternal anxiety or depression, but apparently these aspects of family SES have no impact on maternal psychopathology during pregnancy.

Furthermore, as we hypothesized, negative life events seem to have a greater impact on women when their SES is lower. This more than additional adverse effect of a low SES on the known effect of negative life events on anxiety and depression during pregnancy was never demonstrated before. Only Rich-Edwards et al performed a study to assess the association of a history of abuse with depression during pregnancy in both a rich and a poor part of the city Boston.[103] Despite the higher prevalence of abuse and depression in the more disadvantaged cohort, the associations of abuse with risk of depression were similar in their two cohorts. In our cohort, we found substantial and statistically significant effect modification of the associations of negative life events with both anxiety and depression during pregnancy by SES. The magnitude of the effect modification by SES is larger on the events that have happened more recently. Apparently, low SES has a larger effect on the impact of recent events than to childhood traumas.

Associations of negative life events with adverse obstetric outcomes were observed in large population based studies (low birth weight: N=9,350, preterm birth: N=17,285).[56,57] In our study we found comparable trends, although not statistically significant, possibly due to the smaller sample size. This as well applied for the adverse effect of low SES on obstetric outcomes.[58] To our knowledge, effect modification of adverse effects of negative life events on obstetric outcomes by SES was never studied before. Although most results were not statistically significant, our analyses showed clear trends. Comparable to the effect of life events on symptoms of anxiety and depression, the magnitude of the effect modification by SES may be larger on the events that have happened more recently.

Conclusion

In conclusion, this study suggests that low SES increases the adverse impact of negative life events on anxiety and depressive symptoms in pregnancy and possibly also on birth weight and gestational age. Interventions for anxiety and depression during pregnancy should be targeted particularly to unemployed, less-educated or low-income women who recently experienced negative life events.

CHAPTER 4

Anxiety and depression during pregnancy in Central America: A cross-sectional study among pregnant women in the developing country Nicaragua

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Abstract

Background

Around the world, maternal psychopathology during pregnancy is associated with a range of negative consequences for mother and child. Nevertheless, in Central America the magnitude of this public health problem is still unknown. The objective of this first explorative study was to investigate the prevalence and severity of anxiety and depression during pregnancy in the Central American developing country Nicaragua, as well as the availability of mental health care and to compare with a developed country.

Methods

A population-based cohort of pregnant women in Nicaragua (N=98) was compared with a parallel cohort in the Netherlands (N=4,725) on symptoms of anxiety (Spielberger State Trait Anxiety Inventory) and depression (Edinburgh Postnatal Depression Scale). Associations with the women's the knowledge how to reach professional psychological support were assessed using multivariable linear regression analyses.

Results

Of the Nicaraguan women, 41% had symptoms of anxiety and 57% symptoms of depression, versus 15% and 6% of the Dutch women. Symptom scores of both anxiety and depression were significantly higher in Nicaragua ($p<0.001$). However, only 9.6% of the women indicated that professional psychological help was available for the Nicaraguan pregnant women, which was associated with an increased anxiety score.

Conclusions

In Nicaragua, both prevalence and severity of symptoms of antenatal anxiety and depression are substantially higher than in developed countries. However, availability of psychological help is very limited for pregnant Nicaraguan women. These findings indicate that there is need for further research and support for these women, to prevent negative consequences for both mother and child.

Background

According to the World Health Organization (WHO), mental, neurological, and substance abuse (MNS) disorders are responsible for 14% of the global burden of disease in both men and women.[60] Especially during pregnancy, anxiety and depression are highly prevalent and are known to have a range of serious negative consequences for the child.[14,59,93,104] Experiencing symptoms of anxiety and depression during pregnancy is the most crucial risk factor for having these symptoms in the postpartum period.[47,93] In developed countries, this has been associated with insecure mother-child attachment,[32] preterm birth, low birth weight,[2,12,13] and emotional, cognitive, and behavioural problems in the offspring.[15,93] Ultimately, psychosocial complaints in pregnancy have also been associated with increased maternal mortality.[59,104]

For the developed world, the occurrence of anxiety and depression during pregnancy has been intensively researched. Prevalence studies in developed countries show a prevalence of 10-15% for depression and/or anxiety during pregnancy.[1,2,93,105] Furthermore, research in developed countries shows that anxiety and depression are highly comorbid.[2]

In developing countries, mental health has not received much attention from the research community. Depression and anxiety rates among pregnant women are less well known, but presumably higher. Indeed, it has been estimated that in developing countries, one-in-three to one-in five pregnant women experiences a significant mental health problem, comparing to one-in-ten in developed countries.[59] It is assumed that this high prevalence is the result of lower socioeconomic development of the population, abuse, violence and deficiency in mental health care.[59] The latter is confirmed in the 2011 WHO Mental Health Atlas, which showed that only 36% of people living in low-income countries are covered by mental health care.[106]

To our knowledge, the prevalence of depression and anxiety during pregnancy and their comorbidity are not known for the Central America region. We hypothesize that the prevalence and severity of both anxiety and depression are higher in developing countries than in developed countries. This study aims to explore the occurrence of these common forms of psychopathology among pregnant women in a low-income country in this region, particularly Nicaragua.

Nicaragua is the largest country in Central America, with a population of over six million people and a nominal gross domestic product of $2,006 per capita.[107] Unemployment rate is high, more than 30% of the population has a purchasing power parity of only $2 per day or less, women are low educated, and the majority of the women is illiterate.[108] Although the economic situation seems to improve over the years,[107,108] in healthcare there are still several worrying issues. For example, Nicaragua is one of the few countries

in the world that forbid all abortions, even when a woman's life is in danger.[109] In case this may daunt a pregnant woman: access to mental healthcare is limited, with only 2.92 psychiatrists and psychologists per 100,000 inhabitants, compared to 33.82 per 100,000 in the European developed country the Netherlands.[106]

In this explorative study, we investigated differences in prevalence and severity of anxiety and depression symptoms in pregnant women as assessed in two parallel population based cohorts between Nicaragua and the Netherlands. Additionally, we investigated the correlations between depression and anxiety levels in pregnant women. Furthermore, we discussed the women's the knowledge how to reach mental health professionals and we examined whether this knowledge is associated to the severity of depression and/or anxiety symptoms.

Methods

Study design and participants

The present analyses were carried out using two population-based cohorts: a Nicaraguan cohort and the Pregnancy, Anxiety and Depression (PAD) Study in the Netherlands.

The Nicaraguan cohort consisted of pregnant women who visited the Luis Felipe Moncada public hospital in San Carlos or the community health centres (Centros de Saludes) in San Carlos and Los Chiles, two villages in the rural south of Nicaragua. Women visited the hospital or the community health centre for regular pregnancy consultations or in the final phase of pregnancy. During the inclusion period, July – September 2013, all pregnant women were invited to participate in this cross-sectional study, in which all data were collected anonymously and without follow-up. All 105 women visiting the hospital (N=44, 41.9%) or the participating community health centres (N=61, 58.1%) were asked to join the study, of which 98 were willing to participate (93%). When women were not able to read the questionnaire due to illiteracy (n=54), the researchers or nurses read the questionnaire aloud. We believed this was a better method then excluding all unlettered women. The only women who were excluded from participation were women who had no oral mastery of the Spanish language (N=0). Written informed consent was obtained from each participant. This study was approved by dr. F. Ruiz and dr. M. Romero, directors of both the hospital and the community health centres, on behalf of the Ministry of Health in Nicaragua.

The PAD-study is an ongoing prospective cohort study in the Netherlands which has been set up to investigate symptoms of and risk factors for anxiety or depression during and after pregnancy.[110] As in the Nicaraguan cohort, all pregnant women in their first trimester of pregnancy visiting one of the 109 collaborating primary obstetric care centres and nine hospitals in the Netherlands were invited to participate. The only women who were excluded from participation were women who had shown no mastery of the Dutch language. Non-participation and exclusion were not systematically registered in the PAD-study. Nevertheless, a survey among participating midwives and gynaecologists indicated that the vast majority of them stated that pressure of time meant that they could not hand out the forms to all the visiting women and that they did not specifically invited women they suspected to have symptoms of depression or otherwise. Therefore, we have no reason to believe that responders and non-responders differed in any considerable way with respect to the characteristics relevant to the study.[94] Data used for the present cross-sectional analyses was collected from May 2010 to September 2013. By the end of that period 4,725 women, of whom 4,229 (89.5%) were included in one of the participating midwifery practices and 496 (10.5%) in one of the participating hospitals, had completed the first follow-up questionnaire at 23 weeks GA, including anxiety and depression

questionnaires. The PAD-study was approved by the medical ethical review board of the University Medical Center Groningen.

Measurements

Demographic and pregnancy related variables included in the present study were maternal age and gestational age.

The Spielberger State Trait Anxiety Inventory (STAI) was used to assess the level of anxiety. We used the six-item short-form, because this instrument produces scores similar to those obtained using the full-form, with a lower burden. The cut-off score for an at least moderate level of anxiety is >42 in this short-form.[95] This commonly used questionnaire has a good internal consistency (average Cronbach's alpha of .89).[111]

The 10-item Edinburgh Postnatal Depression Scale (EPDS) was used to assess the level of depressive symptoms.[96] Although the EPDS was originally developed to assess postnatal depression, the questionnaire has demonstrated to reliably assess depressive symptoms during pregnancy as well.[97] The cut-off score for an at least moderate level of depression is ≥12. The 10-item EPDS has shown good internal reliability with a Cronbach's Alpha of 0.82.[112]

In the Nicaraguan cohort, we assessed the women's knowledge how to reach professional support for psychosocial problems (yes/no). We differentiated between support of doctors, nurses, social workers, and psychotherapists. Professional support for psychosocial problems is easily accessible, widely available, and covered by health insurances of practically everyone in the Netherlands. Therefore, it was not assessed in the PAD-study.

Statistics

First, descriptive statistics for demographic and pregnancy related variables were calculated. Differences were tested using independent sample t-tests. Second, the differences in symptom levels of both anxiety and depression between the Nicaraguan and the PAD cohort were assessed using Mann-Whitney U tests because their distributions were skewed. Furthermore we calculated the differences in proportions of women above the cut-off score for an at least moderate level of anxiety (STAI >42) and depression (EPDS ≥12) and tested these differences using Chi^2 tests of independence. Third, a Pearson correlation coefficient was calculated for symptoms of anxiety and depression, for both the Nicaraguan and the PAD cohort.

Finally, in the Nicaraguan cohort we performed logistic regression analyses to quantify the link between the women's knowledge how to reach psychological help (dependent variable) and symptoms of anxiety and

depression during pregnancy (independent variables). For reasons of interpretation we standardized the symptom scores for anxiety and depression to a standard normal distribution, i.e. we created Z-scores. Consequently, the odds ratios obtained from the logistic regression analyses denote the relative increase in the odds of the knowledge how to reach help per standard deviation of symptoms score. To obtain results that can be considered dimension specific, we performed additional analyses in which we adjusted the analyses of anxiety symptoms for the level of depressive symptoms by adding depression symptom level as independent variable, and vice versa. To correct for shared variance, we added maternal age and gestational age as independent variables. Hosmer and Lemeshow goodness-of-fit tests were performed as regression diagnostics, considering $p>0.05$ as a good fit.

All analyses were performed with SPSS 22 (IBM, USA). The level of statistical significance was conventionally set at 0.05, two-sided. All data is available upon request.

Results

As shown in table 1, at the time of completing the questionnaires, mean gestational age of women in the Nicaraguan cohort was 30.6 weeks (SD=9.5, min=8, max=40) and in the PAD study 23.5 weeks (SD=1.9, min=18, max=27). Mean maternal age of the Nicaraguan women was 23.6 years (SD=6.9, min=13, max=43) and 30.7 years (SD=4.5, min=16, max=44) in the Dutch cohort, respectively. Differences in mean gestational and maternal ages were statistically significant ($p<0.001$).

Mean STAI score in the Nicaraguan cohort was 38.7 (median=36.7, SD=13.7, min=20, max=70) and in the PAD study 33.3 (median=33.3, SD 9.7, min 20, max 80). Mann Whitney U, U=174638, $n_1=98$, $n_2=4617$, $p<0.001$. A total of 40 women (41%) had a STAI score above 42 (indicating at least moderate symptoms of anxiety), compared to 699 (15%) in the Netherlands (Chi^2 test of independence $p<0.001$).

Mean EPDS score of the pregnant women in Nicaragua was 12.3 (median=13.0, SD=5.5, min=0, max=25) and in the Netherlands 5.0 (median=4.0, SD=3.7, min=0, max=27). Mann Whitney U, U=64506, $n_1=98$, $n_2=4600$, $p<0.001$. A total of 56 women (57%) had an EPDS score above 11 (indicating at least moderate symptoms of depression), compared to 280 (6%) in the Netherlands (Chi^2 test of independence $p<0.001$).
The STAI- and EPDS-scores were moderately correlated (Pearson's r=0.33, 95% CI=0.14 – 0.52, p=0.001) in Nicaragua and highly correlated in the Netherlands (Pearson's r=0.73, 95% CI=0.71 – 0.75, p<0.001).

In Nicaragua, only 9 of the 94 (9.6%) women who completed this question indicated that professional psychological help is available for them. The STAI score was significantly associated with the knowledge how to reach psychological support (OR=1.361, 95%CI=1.016 – 1.824, p=0.039). Conversely, the EPDS score showed no statistically significant association with this knowledge (OR=1.044, 95%CI=0.785 – 1.045, p=0.623). Adjustment of the analysis of anxiety symptoms for the level of depressive symptoms, and vice versa, as well as adding maternal age and gestational age did not notably affect the results. Finally, repeating all analyses in both illiterate and non-illiterate women showed similar results.

Table 1: Descriptive statistics

	Nicaragua (N=98)	The Netherlands (N=4,725)	p-value
Maternal age in years, mean (SD)	23.6 (6.9)	30.7 (4.5)	<0.001
Gestational age in weeks, mean (SD)	30.6 (9.5)	23.5 (1.9)	<0.001
STAI-score, median (range)	36.7 (20-70)	33.3 (20-80)	<0.001
STAI-score>42, N (%)	40 (41)	699 (15)	<0.001
EPDS-score, median (range)	13.0 (0-25)	4.0 (0-27)	<0.001
EPDS-score>11, N (%)	56 (57)	280 (6)	<0.001

Symptom levels of anxiety and depression were assessed using STAI- (min-max = 20-80) and EPDS-questionnaires (min-max = 0-30) during pregnancy. Cut-off values STAI>42 and EPDS>11 indicate moderate symptom levels of anxiety and depression, respectively.
Differences were tested using independent sample t-tests, Mann-Whitney U tests, and Chi² tests of independence where appropriate.

EPDS – Edinburgh Postnatal Depression Scale, SD – Standard deviation, STAI – Spielberger State Trait Anxiety Inventory.

Discussion

Main findings

In this first explorative study assessing antenatal psychopathology in Central America, we found higher prevalences of anxiety and depression than observed in developed countries. The scores in our Nicaraguan sample were substantially higher than in the Netherlands and this difference was statistically significant. Further, we found a weaker correlation between anxiety and depression scores in Nicaragua than in the Netherlands. Additionally, although there may be psychological help available for the Nicaraguan pregnant women, these women were mostly not aware of this possibility or they were unable to reach this help. We found a significant association between women's knowledge how to reach psychological help for these women and symptoms of anxiety, but not with depression.

Strengths and limitations

The present study is not without limitations. First, both the STAI as the EPDS are self-report questionnaires. Even though these are worldwide commonly used questionnaires, misunderstandings of the questionnaire, possibly due to illiteracy, may have led to over- or under-reporting. Earlier research showed that a lower educational level was associated with a higher rate of psychopathology during pregnancy.[47] Nevertheless, when a participating woman was unlettered, we read the questionnaire aloud. We believed this was a better method then excluding all illiterate women. Furthermore, our analyses showed similar results in both illiterate and non-illiterate women. Secondly, cut-off values for both STAI and EPDS questionnaires may depend on different cultural backgrounds. However, since this is the first study among Nicaraguan women, we considered it justified using the widely recognised cut-off values for an at least moderate level of anxiety (STAI >42) and depression (EPDS ≥12).[95,97] Third, the sample sizes differed strongly between both samples, diminishing statistical power. Nevertheless, we demonstrated statistically significant differences between the Dutch and Nicaraguan groups. Finally, in our longitudinal Dutch cohort, women received multiple questionnaires during pregnancy, including STAI and EPDS questionnaires at 23 weeks gestational age. Our Nicaraguan cohort consisted of women who participated at any moment of pregnancy, with a mean gestational age of 30.6 weeks. The mean gestational age may be comparable (end of second versus start of third trimester), but the SD was increased fivefold.

A strong point is in our view that we were able to include a population-based sample of Nicaraguan pregnant women in a rural area, from both a public hospital and community health centres and had a remarkably high response rate (93%). Because of the use of equal questionnaires in both Nicaragua and

a large sample in the Netherlands, we were able to compare symptomatology of antenatal psychopathology between Nicaragua and a developed country. This study only explored the presence of anxiety and depression and the women's knowledge how to reach psychological help, but since this was the first study on antenatal psychopathology in a rural area in Central America, this publication can be a supplement to the literature on this topic.

Interpretation

With respect to the burden imposed by mental disorders, mental health is known to be an under-researched health area, especially during pregnancy.[113] Although the WHO recognises psychopathology as an important global health problem which causes morbidity and mortality in both mother and child, the problem may be even bigger than earlier thought.[14,59,60,93,104] Most earlier published prevalences of depression and/or anxiety during pregnancy were found in developed countries and were lower compared to those we found in our Nicaraguan sample, namely 10-15%.[1,2,93,105]

Literature demonstrating prevalences of antenatal anxiety and depression in developing countries outside Central America showed various results. For example, in Nigeria a low prevalence of 10.5% for generalized anxiety disorder was found among pregnant women,[114] but the severity and effect of anxiety symptoms (e.g. worry, avoidance, and obsessions) may not always rise to the level of an anxiety disorder diagnosis.[115] In contrast, in Brazil, the prevalence rate of anxious symptoms among pregnant women is estimated to be 60%, and the rate for depressive symptoms was about 20%.[116] Furthermore, in Bangladesh the prevalence rate of depressive symptoms among pregnant women is estimated to be 33% and 42.7% in Pakistan.[117,118] The prevalences of anxiety (41%) and depression (57%) in our sample of Nicaraguan pregnant women were comparable to these earlier studies in developing countries but notably higher than in developed countries.

Unlike in developed countries, where anxiety and depression are highly correlated,[2] in our Nicaraguan sample the observed correlation was substantially lower. Although possibly (partly) caused by the limited sample size, this finding suggests that anxiety and depression may have different origins, more often so in developing countries.
Although we neither performed a longitudinal study nor we searched for causal factors, the results of this first study on this subject in Nicaragua indicate the need for further research. Compared to developed countries, lower education, lower income, younger maternal age, and more negative or traumatic life events could be factors in Nicaragua that relate to a higher risk of suffering from psychopathology during pregnancy.[47,59]
As one of the low-income countries in the Central American region, Nicaragua reported only 1% of the total health care budget is reserved for mental health, and 91% of that is given to psychiatric hospitals.[106] Under this

condition, it is likely that relatively mild mental health issues in a specific population like pregnant women are neglected.
A very small proportion of the women, less than ten percent, indicated that psychological help was available and that they knew how to reach that help. This statement was associated with a higher anxiety score, suggesting that the anxious women know how to find psychological help. This was not the case for the depressive women. In any case, for the women in the rural areas psychological help may not be commonly available, so besides more knowledge about the problems, the possibilities of providing effective treatment if needed, e.g. psychotherapy for antenatal psychopathology, should be explored. It would be desirable to investigate the results of this possible solution in a follow-up study in the same geographical area.

Conclusion

In conclusion, this study suggests that antenatal anxiety and depression in Central America are important public health problems. Both prevalence as severity of symptoms of anxiety and depression during pregnancy are higher than we knew from earlier research. This study indicates that there is need for further research and support for these Nicaraguan women.

CHAPTER 5

Associations of big five personality traits and psychopathology with meeting the WHO recommendation of six months exclusive breastfeeding: a prospective cohort study

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Midwifery (under review)

Abstract

Background

Breastfeeding is widely recognised as the ideal form of infant feeding. The World Health Organization (WHO) recommends that all infants should be exclusively breastfed for the first six months of life. Both symptoms of anxiety and depression and personality traits are associated with exclusive breastfeeding duration. However, associations between personality traits and breastfeeding outcomes might in part be explained by symptoms of anxiety or depression, because links have been established between personality traits and psychopathology, which in turn are associated with breastfeeding. However, this explanation has never been studied.

Methods

We performed a prospective cohort study including 2,927 pregnant women from the general population included in the obstetric care in the Netherlands. We performed logistic regression analyses to test the associations of 'big five' personality traits (NEO Five Factor Inventory), anxiety (State Trait Anxiety Inventory) and depression (Edinburgh Postnatal Depression Scale) symptom levels during pregnancy and postpartum with meeting the WHO recommendation of six months exclusive breastfeeding.

Results

High symptom levels of depression (per EPDS Z-score: OR=0.884, 95%CI=0.794–0983) both during pregnancy and postpartum were statistically significantly associated with not meeting the WHO recommendation. Anxiety was not significantly associated (per STAI Z-score: OR=0.886, 95%CI=0.774–1.014). Of the personality traits, only agreeableness (OR=1.168, 95%CI=1.049–1.300) and openness (OR=1.304, 95%CI=1.174–1.448) were associated with meeting the WHO recommendation. After adjustment for both antenatal and postpartum symptom levels of anxiety and depression, the association of the openness personality trait remained strong and statistically significant (p<0.001).

Conclusions

Our results support independent associations of depression symptom level as well as the openness personality trait with meeting the WHO recommendation on breastfeeding. Patient-centred care should take symptoms of depression and personality into account in an effort to tailor interventions to optimize breastfeeding behaviour.

Background

Breastfeeding is widely recognised as the ideal form of infant feeding.[119] Infants who are exclusively breastfed during the first six months of life experience less gastrointestinal and acute lower respiratory infections than those who are partially breastfed.[120,121] On the longer term, a history of breastfeeding is associated with reduced risks of allergies, asthma, atopic dermatitis, acute otitis media, type I and II diabetes, obesity, childhood leukaemia, and sudden infant death syndrome.[122-124] Additionally, breastfeeding improves mother–infant bonding and secure attachment.[125] Finally, breastfeeding is beneficial for maternal health, as it may reduce the risk of breast cancer, ovarian cancer, and type II diabetes.[126-128]

Because of these profound health benefits for mother and child, the World Health Organization (WHO) recommends that all infants should be exclusively breastfed for the first six months of life.[119] Although women are often aware of the 'breast is best' message,[129] and 63-99% of all women in industrialised countries initiate breastfeeding,[130] many do not exclusively breastfeed their infant or do not continue for six months and therefore do not meet the WHO recommendation.[131] To target and design interventions which promote breastfeeding it is essential to have a clear understanding of the determinants of continuation of breastfeeding to meet this WHO recommendation.

Previous studies into breastfeeding (dis)continuation have revealed maternal age, parity, socioeconomic status and relationship status as possible predictors of the decision to discontinue exclusive breastfeeding before reaching six months.[132] Nevertheless, another study showed that psychological factors such as symptoms of anxiety and depression were more predictive of exclusive breastfeeding duration than these factors combined.[28] Symptoms of anxiety and depression frequently occur during pregnancy and in the postnatal period.[2,47,95,105] Women experiencing these symptoms tend to breastfeed for a shorter period of time and are less likely to exclusively breastfeed.[61,62] However, research examining roles of psychological factors on six months exclusive breastfeeding is scarce.[64]

Other possibly important factors in relation to breastfeeding are the 'big five' personality traits of agreeableness, conscientiousness, extraversion, neuroticism and openness. A number of studies showed positive associations of higher levels of agreeableness, extraversion, and openness with breastfeeding, although these studies were not all methodologically robust.[66-68]

Associations between personality traits and breastfeeding outcomes might in part be explained by symptoms of anxiety or depression, because links have been established between personality traits and psychopathology,[69-72] which in turn are associated with breastfeeding.[61,62] However, this explanation has

never been studied. This prospective cohort study investigates possible independent associations of personality traits and symptom levels of anxiety and depression during pregnancy and the postpartum period with meeting the WHO recommendation of six months exclusive breastfeeding.

Methods

Sample

This study was carried out using measurements from the Pregnancy, Anxiety and Depression (PAD) study.[94] This population-based prospective cohort study was designed to investigate symptoms of and risk factors for antenatal and postpartum anxiety and depression. All pregnant women in their first trimester of pregnancy visiting a total of 109 collaborating primary obstetric care centres and 9 hospitals in the Netherlands were invited to participate. A survey was conducted among participating midwives and gynaecologists to probe inclusion strategies. The results indicated that time constraints were mostly deemed responsible and that they had not specifically invited women they suspected to have risk factors, psychopathology or other conditions. Therefore, we have no reason to believe that responders and non-responders differed in any considerable way with respect to characteristics relevant to the present study. Written informed consent was obtained from each participant. After the baseline questionnaires at the end of the first trimester, follow-up assessments took place at the end of the second and third trimesters, as well as six weeks and three and six months postpartum.

Data used for the present study were collected from May 2010 to May 2015. By the end of that period, 5784 women had completed baseline assessments. Of these, 2,927 women completed breastfeeding assessments 6 months postpartum (response rate 50.6%). Non-responders did not significantly differ from responders on relationship status, occupational status, and postpartum measurements of anxiety and depression symptom levels. However, non-responders were significantly younger (30 versus 31, $p < 0.04$), had a lower socio-economic status (SES; $p < 0.01$), and experienced more symptoms of anxiety and depression during pregnancy ($p < 0.02$).

Measurements

Demographic variables and pregnancy-related variables used in the present study were assessed using online questionnaires and included age, parity, relationship status, and a composite measure of SES. This measure was based on the Leidsche Rijn study and was calculated by equally weighing three aspects of SES: educational level, occupation (yes/no), and family annual gross income.[99] Educational level was defined as the highest completed education, divided into three categories; low (elementary and lower tracts of secondary education), intermediate (higher tracts of secondary education and intermediate vocational education), and high (higher vocational education and university). Family annual gross income was divided into low (€0 – €30,999), modal (€31,000 – €59,999), and high (€60,000 or more).

Personality traits were assessed at baseline, in the third trimester and six months postpartum using the NEO Five Factor Inventory (NEO-FFI).[65,133] The NEO-FFI is a shortened version of the NEO-Personality Inventory-Revised (NEO-PI-R), consists of 60 items, and covers the 'big five' of personality (agreeableness, conscientiousness, extraversion, neuroticism and openness). Responses are provided on a 5-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree).

Symptom levels of anxiety and depression were measured each trimester as well as six weeks and three months postpartum. The Spielberger State Trait Anxiety Inventory (STAI) was used to assess symptom levels of anxiety.[95] We used the 6-item short-form to measure state anxiety which produces scores similar to those obtained using the full-form. The 10-item Edinburgh Postnatal Depression Scale (EPDS) was used to measure depression symptom levels.[96] The used versions of the STAI and the EPDS have both been shown to be valid during and after pregnancy.[95-97]

Breastfeeding status, i.e. meeting the WHO recommendation of providing six months exclusive breastfeeding, was assessed using an online questionnaire at six months postpartum. Exclusive breastfeeding is defined as the infant receiving (expressed) breast milk only and, if necessary, drops and syrups like vitamins, minerals and medicines.[63]

Multiple imputation of missing data

To avoid risk of bias and loss of statistical power in complete case analyses, missing data were imputed. We used multiple imputation by chained equations under the assumption that data was missing at random (MAR) or completely at random (MCAR).[100] Twenty datasets were imputed and combined according to Rubin's rules.[101] The percentage of missing data was approximately 32 (range: 8%; age – 29%; relationship status). The missing data mechanism was studied for each of the variables, by predicting missingness of each of these variables from the other variables in the imputation model using multivariable logistic regression analyses. These analyses showed explained variances ranging from 4.3% to 41.2% (Nagelkerke's R^2), implying that data were at least partly missing at random, and consequently, multiple imputation may have minimized bias. The final imputation model included those variables that predicted the value of the incomplete variable and whether the incomplete variable was missing or not. Because the MAR nor MCAR assumption can be proved we added complete case analyses as a sensitivity analysis.

Data analyses

Descriptive statistics for demographic variables and pregnancy-related variables, personality traits, and symptom levels of anxiety and depression for all measurements during pregnancy and postpartum, as well as the average symptom levels throughout all measurements were calculated according to the likelihood of meeting the WHO recommendation of providing six months exclusive breastfeeding.

Differences between both groups were tested using chi-square and independent samples t-tests where appropriate. Measurements of symptom levels of anxiety and depression exhibiting skewed distributions were transformed using the natural logarithms, before all following analyses were conducted to satisfy the prerequisite assumptions of normality. To allow for valid comparison of effect sizes between the associations with age, anxiety, depression, and personality traits, we created Z-scores for the corresponding variables.

Hereafter, using multivariable linear regression analyses, we assessed the associations of anxiety and depression symptom levels as dependent variables with all five personality traits as independent variables. First, we assessed the associations using all separate measurements of anxiety and depression successively, both during pregnancy and postpartum. Second, we assessed the associations using the average symptom levels.

Furthermore, we assessed the Pearson's r correlation coefficient of the averages of antenatal and postnatal symptom levels of anxiety and depression. Hereafter, the associations between symptom levels of both anxiety and depression with meeting the WHO recommendation of six months exclusive breastfeeding were assessed. To obtain results that can be considered dimension specific, we performed an additional analysis in which we adjusted the analysis of anxiety symptoms for the level of depressive symptoms by adding depression symptom level as independent variable, and vice versa.

Finally, using multivariable logistic regression, we assessed the associations of meeting the WHO recommendation as dependent variable with all five personality traits as independent variables. Subsequently, to assess to what extent the associations could be explained by psychopathology during and after pregnancy, we added the average symptom levels of anxiety and depression as independent variables. All analyses were repeated including potential confounders; age, relationship status, parity, and SES.

Multiple imputation and all analyses were performed with SPSS 22 (IBM, USA). The level of statistical significance was conventionally set at 0.05, two-sided.

Results

Of the study population comprising 2927 women, 447 women (15.3%) were classified as having met the WHO recommendation of providing six months exclusive breastfeeding. A shown in table 1, the majority (N=2,892; 98.8%) had a relationship, was multiparous (N=1,645; 56.2%) and had a high SES (N=1,997; 68.2%). Women who met the WHO recommendation were older (t=-2.357, p=0.018) than those who did not.

Furthermore, women who met the WHO recommendation showed a higher score on the agreeableness domain of the NEO-FFI (t=-2.849, p=0.004) and on the domain of openness (t=-5.010, p<0.001) than women who did not meet the WHO recommendation. No statistically significant differences were found between both groups on the remaining personality traits (conscientiousness, extraversion, and neuroticism). Results were similar for all measurements (first and third trimester, and six months postpartum).

Women who did not meet the WHO recommendation experienced a higher anxiety symptom level (t=2.384, p=0.017) in their first trimester than women who did meet the recommendation. Anxiety symptom levels in the second and third trimester, as well as in the postpartum period did not statistically significantly differ between the groups, and likewise the average anxiety symptom level did not statistically significantly differ. Women who did not meet the WHO recommendation had statistically significantly higher average depression symptom levels (t=2.284, p=0.022), as well as at all trimesters during pregnancy and postpartum.

Table 1: Demographic characteristics of the study population (N=2,927) according to meeting the WHO recommendation of providing six months exclusive breastfeeding.

	Meeting WHO recommendation (N=447)	Not meeting WHO recommendation (N=2,480)	p-value
Age in years, mean (min-max)	31.0 (17-45)	30.5 (21-41)	**0.018**
In a relationship, N (%)	443 (99.1)	2449 (98.8)	0.100
Primiparae, N (%)	174 (38.9)	1108 (44.7)	0.062
Socio-economic status, N (%)			0.206
Low	23 (5.1)	161 (6.5)	
Medium	108 (24.2)	638 (25.7)	
High	316 (70.7)	1681 (67.8)	
Personality traits, mean (SD)			
Agreeableness	5.90 (1.63)	5.69 (1.63)	**0.004**
Conscientiousness	5.46 (1.86)	5.50 (1.74)	0.601
Extraversion	5.51 (1.65)	5.60 (1.61)	0.221
Neuroticism	3.77 (1.69)	3.86 (1.69)	0.267
Openness	5.76 (1.70)	5.40 (1.67)	**<0.001**
Averaged symptom levels			
STAI-score, mean (SD)	31.20 (6.18)	31.76 (6.21)	0.079
EPDS-score, mean (SD)	4.23 (2.47)	4.44 (2.55)	**0.022**

Socio-economic status (SES) consisted of a composite measure in tertiles based on equal weighing of educational level, occupation (yes/no), and family annual gross income. Personality traits according to NEO-FFI (min-max = 1-9). Symptom levels of anxiety and depression were assessed using STAI- (min-max = 20-80) and EPDS-questionnaires (min-max = 0-30) during pregnancy and postpartum and were subsequently averaged. Bold numbers are p<0.05.

SES – Socioeconomic status, SD – Standard deviation, STAI – Spielberger State Trait Anxiety Inventory, EPDS – Edinburgh Postnatal Depression Scale, NEO-FFI – NEO Five Factor Inventory.

Table 2: Associations between personality traits and symptoms of anxiety and depression (N = 2,927).

	Anxiety	Depression
Personality traits		
Agreeableness	-0.196 (-0.223; -0.168)	-0.179 (-0.216; -0.142)
Conscientiousness	-0.231 (-0.257; -0.204)	-0.262 (-0.300; -0.225)
Extraversion	-0.328 (-0.353; -0.303)	-0.357 (-0.394; -0.321)
Neuroticism	0.488 (0.467; 0.510)	0.573 (0.542; 0.605)
Openness	0.064 (0.018; 0.074)	0.071 (0.032; 0.110)

Multivariate linear regression analyses, values are B (95% CI). Symptom levels of anxiety and depression were assessed using STAI- and EPDS-questionnaires during pregnancy and postpartum and were subsequently averaged and standardized by calculating Z-scores. Personality traits according to NEO-FFI. B is coefficient from linear regression. All associations are p≤0.001.

CI – Confidence interval, STAI – Spielberger State Trait Anxiety Inventory, EPDS – Edinburgh Postnatal Depression Scale, NEO-FFI – NEO Five Factor Inventory.

As can be seen in table 2, statistically significant associations were found between all personality traits and average symptom levels of both anxiety and depression (all *p*'s ≤ 0.001). These associations were similar for all anxiety and depression measurements, both during and after pregnancy (data not shown). The personality traits of agreeableness, conscientiousness and extraversion were negatively associated with symptoms of anxiety (B's = -0.196; -0,231; -0.328) and depression (B's = -0,179; -0.262; -0.357). The personality traits of neuroticism and openness showed positive associations with both anxiety (B's = 0.488; 0.064) and depression (B's = 0.573; 0.071).

Symptoms of anxiety and depression were highly correlated (Pearson's r = 0.765). As shown in table 3, the average depressive symptom level but not the average anxiety symptom level was statistically significantly associated with meeting the WHO recommendation (p=0.023). Per Z-score of the EPDS questionnaire the odds of meeting the WHO recommendation decreased with 11.2% (OR=0.884, 95%CI=0.794; 0.983). After correction for anxiety symptom level, the association of depression symptom level lost its statistical significance (p=0.113).

Furthermore, per Z-score of the agreeableness trait the odds of meeting the WHO recommendation increased with 16.8% (OR = 1.168, 95%CI = 1.049; 1.300) and of the openness trait 30.4% (OR = 1.304, 95%CI = 1.174; 1.448). After adjustment for symptom levels of anxiety or depression the positive effect of agreeableness diminished, but the effect of openness remained stable (p < 0.001). The remaining personality traits were negatively associated with meeting the WHO recommendation, but these associations were small and not statistically significant.

When repeating the analyses including all confounders, similar results were found. Results of complete case analyses were not notably different from imputed data analyses.

Table 3: Associations between personality traits and meeting the WHO recommendation of providing six months exclusive breastfeeding (N = 2,927).

	Unadjusted	Adjusted for symptoms of anxiety	Adjusted for symptoms of depression
Anxiety level	0.886 (0.774; 1.014)		0.959 (0.812; 1.133)
Depression level	**0.884** (0.794; 0983)	0.900 (0.789; 1.026)	
Personality traits			
Agreeableness	**1.168** (1.049; 1.300)	0.930 (0.808; 1.070)	0.905 (0.813; 1.008)
Conscientiousness	0.973 (0.877; 1.079)		
Extraversion	0.937 (0.845; 1.040)		
Neuroticism	0.943 (0.851; 1.046)		
Openness	**1.304** (1.174; 1.448)	**1.313** (1.182; 1.458)	**1.318** (1.186; 1.464)

Values are OR (95% CI). Symptom levels of anxiety and depression were assessed using STAI- and EPDS-questionnaires during pregnancy and postpartum and were subsequently averaged and standardized by calculating Z-scores. Personality traits according to NEO-FFI. Bold numbers are p<0.05

OR – Odds ratio, CI – Confidence interval, STAI – Spielberger State Trait Anxiety Inventory, EPDS – Edinburgh Postnatal Depression Scale, NEO-FFI – NEO Five Factor Inventory.

Discussion

Main findings

In this large population based prospective cohort study we found associations of both symptom levels of depression during and after pregnancy and the personality trait of openness with meeting the WHO recommendation of six months exclusive breastfeeding. The latter was only partly explained by symptom levels of anxiety and depression. Therefore, mediation of this association may be largely caused by a direct effect of the openness personality trait on continuation of breastfeeding. To target and design interventions aimed at exclusive breastfeeding continuation, it is essential that both personality traits and symptoms of anxiety and depression are acknowledged as important determinants. Both decrease of anxiety and depression symptom levels and personality changes may aid in meeting the WHO recommendation.

Strengths and limitations

A few limitations of this study need to be considered. First, measurements of symptoms of anxiety and depression were based on self-report questionnaires. No diagnosis could be made using these questionnaires, although both STAI and EPDS questionnaires are commonly used in identifying symptoms of psychopathology.[95-97] Second, of the 5784 women who had completed baseline assessments, only 2927 women (50.6%) completed breastfeeding assessments 6 months postpartum. Non-responders were younger, had a lower SES, and experienced more symptoms of anxiety and depression during pregnancy but did not significantly differ from responders on relationship status, occupational status, and postpartum measurements of anxiety and depression. Nevertheless, this follow-up rate may decrease generalizability.

These limitations are potentially offset by strengths of this study. Our sample size was considerable and as far as we know one of the largest in this field. The inclusion of this large population based prospective sample of women living in a large part of the Netherlands, in both rural and urban areas, may have enhanced the study's precision and generalizability. Additionally, in contrast to earlier studies, in the present study we adjusted our analyses on the associations of personality traits with meeting the WHO recommendation for anxiety and depression symptom levels.

Interpretation

Although a recent review concluded that there is very limited research examining the role of symptoms of anxiety and depression on exclusive

breastfeeding to six months duration,[64] we found significant lower symptom levels of anxiety (first trimester only, p = 0.017) and depression (during pregnancy and postpartum, p = 0.022) in women who met the WHO recommendation than in women who did not. However, statistically significant, the observed differences between the groups were subtle. Additionally, because the association of average depression symptom level with meeting the WHO recommendation lost its statistical significance after correction for average anxiety symptom level, the association of depression should not be considered as independent of anxiety. Nevertheless, the results of our analyses on the openness personality trait only showed a partly explanation by anxiety and depression symptom level. The direct effect remained strong and significant, suggesting that this personality trait is directly associated with meeting the WHO recommendation, independently of symptoms of depression.

Earlier studies on the association of personality traits with breastfeeding initiation in the United States (n = 87)[66] and with breastfeeding duration in the United Kingdom (n = 602) [67,68] showed associations between high conscientiousness,[67,68] high extraversion,[66-68] low neuroticism,[67,68] and high openness[66] with breastfeeding. After adjustment for symptoms of anxiety and depression, we only found a significant association of high openness (OR's = 1.304 – 1.318) with reaching the WHO recommendation of providing six months exclusive breastfeeding. Our findings suggest that women who succeed in providing breastfeeding for six months might be more open to new experiences and appear to be more outgoing, seeking novelty and variety.

Furthermore, earlier studies on different subjects suggested that openness influences the processes of receiving information and decision-making. Individuals who showed high scores in openness found it easier to accept information and were more prone to choose the options for protection than people with other dominant personality traits.[134,135] Thus, women with high levels of openness may accept information about breastfeeding more easily, and may choose for protection of their infant compared to women with lower levels of openness. This may be an explanation why women with higher scales of openness are more likely to meet the WHO recommendation.

Our findings that personality traits are associated with psychopathology are in line with earlier research conducted both in pregnant women[71,72] and in the general population.[69,70] In our sample, low agreeableness, low conscientiousness, low extraversion, high neuroticism and high openness were associated with symptoms of both anxiety and depression during pregnancy and postpartum. Earlier research was somewhat inconclusive about which trait is associated with psychopathology. Two studies among pregnant women in China (n = 292)[71] and in Sweden (n = 1037)[72] and showed that low agreeableness,[71] low consciousness,[71] and high neuroticism[71,72] seemed to be associated with symptoms of depression. No

associations were seen with extraversion and openness, which may be explained by their smaller sample sizes. In a large meta-analysis in the general population, low conscientiousness, low extraversion, and high neuroticism were associated with major depressive disorder and general anxiety disorder.[70] No associations with agreeableness and openness were observed, possibly because psychiatric disorders were used as outcome measures. In contrast, in our study we used symptom level scores to include differences in subclinical symptoms. These symptom level scores were also used in a recent meta-analysis in which the associations between personality traits of the five-factor model and risk of depressive symptoms were assessed in general population.[69] Our results correspond to theirs, suggesting that the associations between personality traits with both anxiety and depression symptoms are similar in pregnant and non-pregnant women.

Initiating and continuing breastfeeding has significant health benefits for the infant,[119-125] as well as for the mother.[126-128] Promoting the initiation and continuation of breastfeeding and providing adequate support when a breastfeeding woman experiences problems is therefore important. There are numerous interventions concerning breastfeeding, which may help women initiate breastfeeding and prevent women from stopping breastfeeding when they encounter problems.[136,137] Targeting enhancing openness and treating depression in the antenatal and or postnatal period, for instance by reinforcing new experiences, role models that emphasize that breastfeeding is a new experience that might be initially a hassle, while later just becomes a normal daily routine, might improve initiation and continuation of breastfeeding. Earlier research demonstrated that subtle change in personality traits may be effected.[138,139] More research is needed to assess whether tailored personality-specific interventions to improve breastfeeding may be more effective.

Conclusion

In conclusion, we found evidence that symptom levels of depression but not of anxiety both during pregnancy as postpartum are associated with meeting the WHO recommendation of providing six months exclusive breastfeeding. Likewise, the openness personality trait was associated with meeting the WHO recommendation on breastfeeding, even when adjusted for anxiety and depression symptom levels during pregnancy and postpartum. Patient-centred care should take personality into account in an effort to tailor interventions to optimize breastfeeding behaviour.

CHAPTER 6

Postpartum depression predicts offspring mental health problems in adolescence independently of parental lifetime psychopathology

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Abstract

Background

Postpartum depression (PPD) follows 5–15% of the life births and forms a major threat to the child's mental health and psychosocial development. However, the nature, continuance, and mediators of the association of postpartum depression (PPD) with the child's mental health are not well understood. The aim of this study was to investigate whether an association between PPD and adolescent mental problems is explained by parental psychopathology and whether the association shows specificity to the internalizing or externalizing domain.

Methods

2729 adolescents aged 10–15 years from the TRacking Adolescents' Individual Life Survey (TRAILS) were included. Both PPD and parental lifetime history of psychopathology were assessed by parent report. Adolescents' psychopathology was assessed using the Achenbach scales (parent, teacher and self-report). Linear regression was used to examine the association between PPD and adolescent mental health.

Results

We found a statistically significant association of adolescents' internalizing problems with maternal PPD, which remained when adjusted for parental psychopathology. We found no association for externalizing problems.

Conclusions

The association of PPD with internalizing but not externalizing problems extends into adolescence. Parental psychopathology does not explain this association suggesting a direct psychological effect on the child postpartum. If this effect appears causal, early treatment of parental psychopathology may prevent internalizing psychopathology in the offspring, ultimately in adolescence.

Background

Women frequently suffer from mood changes postpartum. When these escalate, a postpartum depression (PPD) may develop.[140] With its high frequency, i.e. following approximately 5–15% of live births, and its substantial negative effects, PPD is a considerable public health problem.[140-145] Negative effects of PPD not only concern the affected women themselves, but also their offspring.[29,146-153]

Earlier studies have shown that women who suffer from PPD express more negative emotions and are less sensitively attuned to their infants.[33] This may have specific consequences for the child, e.g. attachment insecurity,[34-36] delay in emotional development,[37] social and interaction difficulties,[38] and an increased risk of developing violent behaviour.[39] Several psychological mechanisms underlying these consequences have been suggested including deficient mother–infant attachment,[34-36] and temperamental alterations.[154]

Although PPD is associated with mental health problems in childhood, it is largely unknown to what extent this association is causal in that the depression negatively affects the child during the postpartum period.[155] A non-causal association between PPD and mental health problems in the child may be produced in at least three ways. First, shared genetic liability to psychopathology between mother and child may cause an indirect non-causal association between PPD and the child's mental health. Second, PPD is associated with maternal[40] and possibly also with paternal[156] psychopathology after the postnatal period, both of which may threaten the child's mental health up to adolescence.[41] Third, numerous studies have shown an association between anxiety, stress, or depression during pregnancy and childhood emotional and behavioural problems.[157] In addition to the causality issue, there is debate whether negative effects extend into adolescence and whether the effects regard predominantly internalizing or externalizing mental health problems.[37,40-44]

The aim of this study was therefore to investigate whether the association between PPD and the child's psychopathology extends into adolescence, whether it is specific to the internalizing or externalizing domain of psychopathology and whether the association could be explained by parental psychopathology outside the postpartum period.

Methods

Sample

The TRacking Adolescents' Individual Lives Survey (TRAILS) is a prospective cohort study of Dutch (pre)adolescents, with the aim to chart and explain the development of mental health from preadolescence into adulthood, both at the level of psychopathology and the levels of underlying vulnerability and environmental risk.[158] The TRAILS study was approved by the Central Committee on Research Involving Human Subjects (Dutch CCMO). The present study involves data from the first (T1) and second (T2) assessment wave of the population-based cohort of TRAILS, which ran from, respectively, March 2001 to July 2002, and September 2003 to December 2004. In addition, data from the first (T1) and second (T2) assessment wave of the clinical cohort (TRAILS-CC) were used. These waves ran from September 2004 to December 2005, and September 2006 to November 2007.

Sample selection of the general population concerned five municipalities in the North of The Netherlands, including both urban and rural areas. They were requested to give names and addresses of all inhabitants born between 10-01-1989 and 09-30-1991. Of all children approached for enrolment in the general population cohort (i.e., selected by the municipalities and attending a school that was willing to participate, N=3145), 6.7% (N=211) were excluded because of mental or physical incapability or language problems. Of the remaining 2935 children, 74.5% (N=2188, mean age=11.09, SD=0.56, range 10.0–12.0, 50.8% girls) were enrolled in the study (i.e., both child and parent agreed to participate). Responders and non-responders did not differ with respect to the prevalence of teacher-rated problem behaviour, nor regarding associations between socio-demographic variables and mental health outcomes.[159]

Of the 2230 baseline general-population participants, 96.4% (N=2149) participated in the first follow-up assessment (T2), which was held two to three years after T1. Mean age at T2 was 13.6 (SD=0.53, range=12.0–15.0).

Sample selection of TRAILS-CC is running in parallel with the TRAILS general population cohort. The cohort includes children who have been referred at least once to the child psychiatric outpatient clinic of the University Medical Center Groningen at any point in their life. Measurements and procedures in TRAILS-CC are identical to those in the general population cohort.[158] As expected, non-response in the clinical cohort was higher than in the population-based cohort. Of the 1264 children, who were eligible to enter the clinical cohort, 42.8% (N=541, mean age=11.1, SD=0.50, range 10.0–12.0, 34% girls) were enrolled in the study (i.e., both child and parent agreed to participate). There were again no significant differences between responders and non-responders in age, gender, level of

education of the parents and age at referral to the clinic. Also did these groups not differ on psychopathology subscales and language performance.[158]

Of the 543 baseline participants in the clinical cohort, 85% (N=463) participated in the first follow-up assessment (T2), which was held two years after T1. Mean age at T2 was 12.87 (SD=0.62, range=12.0–15.0).

Measurements

At T1, well-trained interviewers (university graduates, who were extensively trained in interviewing skills, study background and interview content) visited one of the parents or guardians (preferably the mother, 95.6%) at their homes to administer an interview after a complete description of the study was given and written informed consent was obtained from participants. This interview covered a wide range of topics, including developmental history and somatic health, parental psychopathology (to control for recent episodes of depression) and care utilization. Besides the interview, the parent was asked to fill out a self-report questionnaire. Children in the general population cohort filled out questionnaires at school, in the classroom, under the supervision of one or more TRAILS assistants. In the clinical cohort the children visited the outpatient clinic of the University Medical Center Groningen to fill out the questionnaires. Teachers were asked to fill out a brief questionnaire for all TRAILS-children in their class. T2 involved only questionnaires, to be filled out by the children, their parents and their teachers. As in T1, the adolescents completed their questionnaires at school, respectively at the outpatient clinic. Measures that were used in the present study are described more extensively below.

Variables used

Both PPD and parental loading of psychopathology were assessed at baseline (T1) by parent report. The mother was asked whether she had suffered PPD in the first month postnatal, irrespective of having been treated for her condition. To allow adjustment for parental psychopathology outside the postpartum period, we calculated variables representing parental loading of psychopathology as follows. Lifetime parental psychopathology was assessed by means of the TRAILS Family History Interview (FHI).[160] The FHI assessed five dimensions of psychopathology: depression, anxiety, substance dependence, persistent antisocial behaviour, and psychosis. Each dimension was introduced by a vignette (available on request) describing the main DSM-IV characteristics of the dimension, followed by a series of questions assessing lifetime occurrence, professional treatment, and medication use. Information on both biological parents was obtained using a single informant (often the mother). For each dimension, we assigned each parent

to one of the following categories: 0=(probably) never had an episode, 1=(probably) yes, or 2=yes and treatment and/or medication. The prevalence rates in mothers and fathers respectively were: depression (27% and 15%), anxiety (16% and 6%), substance dependence (3% and 7%), and for antisocial behaviour (3% and 7%). We calculated parental loadings for the domains of internalizing and externalizing disorders separately. Both are effectively a count of the number of lifetime disorders within each domain reported by the biological parents. Parental loading on internalizing disorders included depression and anxiety and parental loading on externalizing disorders included substance dependence and persistent antisocial behaviour.[160] The empirical justification for the construction of the familial loadings is twofold (data available on request). First, disorders within each domain were more strongly correlated (on average 0.34) than disorders across domains (0.12), for mothers as well as fathers. Factor analysis of the disorder correlation matrix, for fathers and mothers separately, yielded two factors of internalizing and externalizing problems.[160] These were similar to the two-dimensional structure of common mental disorders.[161] Secondly, the pattern of associations between parental disorders and offspring psychopathology was similar for fathers and mothers, suggesting that the paternal and maternal indices could be combined without obscuring relevant details. In line with this also is that paternal disorders were weakly correlated with maternal disorders. For instance, paternal and maternal depression were associated (0.18) and so were paternal and maternal antisocial behaviour (0.26).[160]

At T1 and T2, the parents completed the Child Behaviour Checklist (CBCL).[162,163] It contains a list of 120 behavioural and emotional problems, which could be rated as 0=not true, 1=somewhat/sometimes true, or 2=very/often true in the past 6 months. Adolescents filled out the self-report version of the CBCL, the Youth Self-Report (YSR)[164,165] and teachers used the Teacher's Checklist of Psychopathology (TCP) based on the Teacher Report Form (TRF).[166] Internalizing and externalizing psychopathology in the adolescents was registered using the combined, equally weighted scores on the Achenbach scales from the children themselves, their parents and their teachers.[162] Combining different sources reduces bias in the prediction of mental health problems and provides more accurate diagnoses than when a single source is used.[167]

The following potential confounders were assessed by parent report: smoking (none, less than 1 cigarette per day, 1–10 per day, 11–20 per day, 1–2 packs per day, more than 2 packs per day)[168] and alcohol use during pregnancy (none, less than 1 unit per week, 1–3 units per week, 4–10 per week, 10–20 per week more than 20 per week), socio economic position (SEP) and obstetric factors. SEP included education, income and occupation of both parents, using the International Standard Classification of Occupations.[169] We created a SEP variable by standardizing and averaging

the items. Obstetric factors included in our analyses were gestational age, mode of delivery, birth weight and admission to neonatal care.

Statistical analyses

We calculated descriptive statistics for all variables. We created purified measures of psychopathology by partialling out shared variance between internalizing and externalizing problems. All variables, except for maternal PPD, were transformed to Z-scores. We averaged the scores of children's psychopathology obtained at T1 and T2 for reasons of statistical stability and our interest in the level of psychopathology rather than change over time. In addition, preliminary analyses showed no major differences between T1 and T2 scores (Cohen's d denoting effect size for all dimensions<0.2). Subsequent analyses were performed using multiple linear regression. First, we assessed the unadjusted associations between PPD and both internalizing and externalizing problems in the adolescent offspring. Second, we adjusted these associations for dimension-specific parental loading and assessed the extent of decrease in the coefficient for PPD. These adjustments were made to investigate to what extent the association between PPD and psychopathology in the adolescent offspring could be explained by a parental history of psychopathology and with that the genetic transmission of mental health problems.

In addition, we performed analyses while adjusting for potential confounders, i.e., smoking and alcohol use during pregnancy, SEP and obstetric factors. Finally, we adjusted for cohort, i.e. general population or clinical cohort. The level of significance was set at 0.05, two-sided. Data were analysed using SPSS 16.

Results

Table 1 shows the descriptive statistics of the main variables we used in this study, divided by the presence or absence of maternal PPD. Seventy-five (2.7%) of the mothers of the adolescents reported a history of a maternal PPD. The demographic statistics show no difference between the children with and without maternal PPD. For both internalizing and externalizing pathology, the distribution was shifted towards the PPD group. This held for parental history as well as adolescent psychopathology.

Table 2 shows a significantly higher level of internalizing problems in adolescents with a history of maternal PPD compared to those without. When adjusted for parental loading the association reduced but remained substantial and statistically significant (difference in z-score: 0.18 (95% CI: 0.04–0.31)).

Table 3 shows no statistically significant association of maternal PPD with externalizing psychopathology in adolescents.

When we adjusted for the potential confounders smoking or drinking during pregnancy, SEP and obstetric factors the association of PPD with either internalizing or externalizing adolescent psychopathology did not materially change. Likewise, adjustment for cohort (general population vs. clinical cohort) did not affect the results.

Table 1: Descriptive statistics according to the presence of a history of maternal postpartum depression (PPD).

	PPD absent (N=2654)	**PPD present (N=75)**
Female gender, N (%)	1336 (50)	37 (49)
Age in years at baseline, mean (SD, range)	11.1 (0.55, 10.0-12.0)	11.1 (0.52, 10.0-12.0)
Internalising psychopathology*, mean (Z-score, SD)	0.4 (0.0, 0.6)	0.6 (0.3-0.7)
Externalising psychopathology*, mean (Z-scores, SD)	0.4 (0.0, 0.7)	0.5 (0.2, 0.7)
Parental lifetime history of internalising psychopathology, N (%)	1187 (45)	70 (93)
Parental lifetime history of externalising psychopathology, N (%)	432 (16)	18 (24)

** Internalising and externalising psychopathology according to the Achenbach scales (mean of parent, teacher and self-report).*

Table 2: Internalising psychopathology* in offspring as predicted by maternal postpartum depression, unadjusted (2.1) and adjusted (2.2) for parental loading for internalising psychopathology.

	B (95% CI)	Standard error	t	p-value
2.1:				
Maternal postnatal depression	0.28 (0.14–0.41)	0.07	4.000	<0.001
2.2:				
Maternal postnatal depression	0.18 (0.04–0.31)	0.07	2.506	0.012
Parental loading for internalising problems	0.09 (0.07–0.11)	0.01	7.735	<0.001

** Shared variance with externalising problems was partialled out.*

Table 3: Externalising psychopathology* in offspring as predicted by maternal postpartum depression, unadjusted (3.1) and adjusted (2.2) for parental loading for externalising psychopathology.

	B (95% CI)	Standard error	t	p-value
3.1				
Maternal postnatal depression	0.00 (-0.14–0.15)	0.07	0.051	0.960
3.2				
Maternal postnatal depression	0.00 (-0.14–0.15)	0.07	0.053	0.958
Parental loading for externalising problems	0.10 (0.07–0.12)	0.01	8.02	<0.001

** Shared variance with internalising problems was partialled out.*

Discussion

Main findings

We investigated the link between PPD and offspring mental health problems in adolescence. For internalizing problems we showed that this relationship extends into adolescence and is only partially explained by parental loading. The relationship appeared to be specific for internalizing problems because there was no association with externalizing problems.

Strengths and limitations

A major asset of this study is that the analyses could be repeated while adjusting for lifetime parental psychopathology. This allowed us to investigate the hypothesis that PPD has a direct effect on the child, separate from psychopathology outside the postpartum period. Another major strength of this study is the use of widely validated composite Achenbach measures of psychopathology based on multiple informants (parent, teacher, child) causing information bias to be limited and reliability to increase.[41] Finally, because of the inclusion of a large population based prospective sample and a high participation rate, our findings have high precision and generalizability.

The findings of this study should be interpreted in the light of three limitations. First, as we already mentioned, the parental loadings for psychopathology are rough approximations of genetic loading and include environmental risk for decreased mental health as well. Nevertheless, the relevance of this potential limitation is questionable as recent findings suggest that the genetic basis for the intergenerational transmission of depression is absent.[170,171] Second, we did not interview each biological parent in person but interviewed only one parent directly and used this parent as informant for the other parent. Therefore, we assume there is underreporting of lifetime parental psychopathology. Third, it was not registered which adolescents belonged to the same family, so a possible effect related to the rank of the child could not be studied.

Interpretation

Earlier studies have indicated that PPD may increase the risk of emotional and behavioural problems in early childhood.[33-37,150,153,156] However, there is debate whether negative effects of PPD are lasting and extend into adolescence and what these effects are.[37,40-44] A commonly recognized limitation was the absence of correction for parental lifetime history of psychopathology, thus leaving the possibility that the association is due to liability shared by mother and offspring.[41] In our study we have overcome

these limitations by correcting for dimension-specific parental loading for psychopathology. Parental loading constitutes a rough approximation of genetic loading and includes environmental risk for decreased mental health, e.g. demographic and socio-economic factors.[160] The observation that in our study the association between PPD and internalizing problems held up after adjustment for maternal internalizing psychopathology outside the postpartum period pleads for a direct psychological effect of PPD. Such a direct psychological effect may be the result of impaired mother–child interaction which has shown to lead to suboptimal attachment.[33,149-153] Alternative explanations of the association of PPD with mental health problems in the offspring include neglect or even abuse of the child[172] or reduced frequency of breastfeeding.[173]

We found no association between PPD and offspring externalizing problems, which does not agree with findings by Fihrer et al. who observed an increased risk for both internalizing and externalizing problems[150] and by Hay and colleagues who reported on an association between PPD and violent behaviour in offspring.[39] This might be explained by the fact that the latter study assessed overt seriously violent behaviour according to DSM-IV criteria only. In contrast, we measured the entire spectrum of externalizing psychopathology as it exists in the general population for which an association with PPD may be weaker. In addition, our findings of raised rates of internalizing problems and no raised rates of externalizing problems are entirely consistent with the recent study of Murray et al.[44]

In our study we found that 2.7% of the mothers had a history of PPD. Recent studies estimated a PPD prevalence of 5–15% of all live births.[141,143-145] We have three possible explanations for this difference. First, in our questionnaire we defined PPD as a depression with an onset within one month after childbirth, while some other studies used an onset within one year. Second, the level of parental education was higher in our study than in the general population,[158] which may explain the lower than expected frequency of PPD. Third, because PPD is retrospectively assessed at T1, its recall may have been incomplete. Nevertheless, in accordance with Hardt and Rutter who stated that retrospectively assessed adverse experiences involve false negatives but rarely false positives,[174] in our study it is quite likely that those women who did report PPD actually had suffered PPD while an unknown number of women who actually suffered PPD did not report it. Consequently, the association between maternal PPD and psychopathology may have been diluted by non-differential determinant misclassification, i.e. recall of PPD was likely independent of the presence of the adolescents' mental health problems. Therefore, the real association may be stronger than we observed.

Conclusion

The association between PPD and psychopathology in the offspring extends into adolescence, is limited to internalizing problems, and is only partially explained by parental lifetime psychopathology. Therefore, mediation of this association may be largely caused by a direct psychological effect on the child in the postpartum period, e.g. as a result of impaired mother–child attachment.

Early screening for and treatment of maternal PPD may decrease the symptoms of PPD[175-177] and, if the association appears causal, may thereby prevent internalizing psychopathology in the offspring, ultimately in adolescence.[178] In addition, because early management of psychopathology in adolescence may reduce symptoms,[179,180] the offspring of mothers with a history of PPD could be monitored more closely for internalizing problems in early adolescence.

PART II

Randomised controlled trial

CHAPTER 7

PRegnancy Outcomes after a Maternity Intervention for Stressful EmotionS (PROMISES): a randomised controlled trial

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and Advances in Neurobiology 2015; 10: 443–459.

Abstract

Background

There is ample evidence from observational prospective studies that maternal depression or anxiety during pregnancy is a risk factor for adverse psychosocial outcomes in the offspring. However, to date no previous study has demonstrated that treatment of depressive or anxious symptoms in pregnancy actually could prevent psychosocial problems in children. Preventing psychosocial problems in children will eventually bring down the huge public health burden of mental disease. The main objective of this study is to assess the effects of cognitive behavioural therapy in pregnant women with symptoms of anxiety or depression on the child's development as well as behavioural and emotional problems. In addition, we aim to study its effects maternal mental health and perinatal outcomes, as well as the cost-effectiveness of cognitive behavioural therapy relative to usual care.

Study design

We will include 300 women with at least moderate levels of anxiety or depression at the end of the first trimester of pregnancy. By including 300 women we will be able to demonstrate effect sizes of 0.35 or over on the total problems scale of the child behavioural checklist 1.5-5 with alpha 5% and power (1-beta) 80%. Women in the intervention arm are offered 10-14 individual cognitive behavioural therapy sessions, 6-10 sessions during pregnancy and 4-8 sessions after delivery (once a week). Women in the control group receive care as usual.

Primary outcome is behavioural/emotional problems at 1.5 years of age as assessed by the total problems scale of the child behaviour checklist 1.5 – 5 years. Secondary outcomes are mental, psychomotor and behavioural development of the child at age 18 months according to the Bayley scales, maternal anxiety and depression during pregnancy and postpartum, and perinatal outcomes such as birth weight, gestational age and Apgar score, health care consumption and general health status (economic evaluation). Trial Registration: NTR2242

Background

The burden of mental disorders is huge and at least comparable to the burden caused by many severe physical diseases. In the WHO Global Burden of Disease project it was estimated that 50% of all daily adjusted life years (DALY's) in the 15-44 years old are due to nine psychiatry-related conditions.[181] Depressive disorders are projected to rank second on a list of 15 major diseases in terms of burden of disease in 2030.[182] In addition, a substantial part of the costs are caused by new cases, which accounts for 39.2% of the costs at population level.[183] Therefore, prevention of mental disorders is essential.

Maternal anxiety or depression during pregnancy is an important and potentially modifiable risk factor for cognitive, behavioural and emotional problems among the offspring children.[15-20] Around 10-20% of all women are suffering from depression or anxiety during pregnancy.[1,93,184,185] The magnitude of the effects of maternal anxiety or depression on the child's psychosocial problems is considerable: it is estimated that up to 22% of the variance in behavioural problems is linked with antenatal anxiety, stress or depression.[19] The adverse effects seem to be lasting. For example, antenatal anxiety of the mother was related to behavioural or emotional problems of 4 year old children, independent of the mother's postnatal depression or anxiety,[15] and higher anxiety levels of the mothers early in pregnancy were related to an increase in ADHD and other externalizing problems in their 8-9 year old children.[186]

There are several mechanisms through which depression or anxiety during pregnancy could have an adverse effect on the offspring. These mechanisms can be divided into direct and indirect. A direct mechanism that has been researched for decades is one in which depression or anxiety activates the maternal stress system leading to elevated glucocorticoid levels, which subsequently influence the development and long-term physiology of the foetus' brain by passing the placenta. This direct mechanism falls under the rubric of "early life programming" and has been a popular hypothesis for the explanation of not only brain disorders but has been suggested to play a role in cardiovascular disease as well.[22] Further, epigenetic variation has been proposed as a mediating mechanism in linking early life exposures to long-term psychological and behavioural outcomes.[23]

The effect of maternal stress on the developing foetus might also be indirect. Women who suffer from antenatal psychopathology have the tendency to take less good care of themselves (e.g. neglecting personal hygiene, the occurrence of sleeping problems, disturbed drinking and smoking habits, denying prenatal care). These consequences might all influence the development of the foetus.[24-27] Another indirect way in which depression might influence the mental development of the offspring is when the antenatal anxiety of depression remains after delivery and turns into

postnatal anxiety or depression. In this way, mother-child attachment might be endangered, because the mother has a reduced ability to respond to the child. Children from depressed mothers have a higher risk of insecure attachment, which in turn is associated with cognitive, behavioural and emotional problems.[30-32,181] In addition, the association between antenatal psychopathology and adverse outcomes in the offspring might be indirect because it could be explained by a shared genetic predisposition between mother and child.

Whatever the actual mechanisms involved are, there is presently convincing evidence that children whose mothers suffered from anxiety or depression during pregnancy constitute a high risk group for behavioural and emotional problems. On population level, substantial total mental health gains may be accomplished when depressed or anxious women are adequately treated during their pregnancy, even if the effect size of the treatment is relatively small.

The effectiveness of psychological therapy in the treatment of both depression and anxiety has been shown during the past 50 years, especially for cognitive behavioural therapy (CBT).[83,90,187-189] Although guidelines state that medication is an alternative effective treatment, the safety of antidepressants during pregnancy remains insecure.[190]

Still, it is too early to implement CBT for depressed or anxious women to prevent psychosocial problems in the offspring. This is because in the development of such a preventive strategy, demonstration of the causality and size of the effect of the reduction of symptoms of depression and anxiety on child outcomes is a crucial step, a step that has not been taken to date. This knowledge gap will be filled by the results of the present experimental study.

We are currently performing a randomised controlled trial (RCT) among pregnant women with symptoms of depression or anxiety to study the effect of CBT as compared to care as usual (CAU) on the offspring's behavioural and emotional problems. In the CBT arm, we expect more beneficial perinatal outcomes, in particular higher birth weight and less prematurity, which are risk factors for adverse cognitive and behavioural outcomes themselves.[16] We also anticipate reduced smoking and less drinking, with many physical and mental health benefits for the child as a result.[27] Since prenatal depression has shown to be related to postnatal depression, we hypothesize that our intervention will also counter postnatal depression, which in turn will benefit the mother – child attachment.[191]

Finally, but not unimportantly, the reduction of symptoms of anxiety or depression during pregnancy and the early postnatal period is valuable in itself. CBT may further provide for a safer approach to reducing symptoms in pregnancy than antidepressant medication.[190] To date, no such study has been performed as far as we are aware of.

Design

Objective

The aim of the present study is to examine the effect of CBT in women with at least moderate symptoms of anxiety and/or depression at the end of the first trimester of pregnancy, on the extent of total behavioural and emotional problems in their children at 1.5 years of age, as compared with CAU.

Setting

The source population consists of all pregnant women in the Netherlands in the first trimester of their pregnancy. Women are recruited in primary, secondary and tertiary obstetric care. Women are screened for anxiety and depression symptoms at the end of the first trimester of pregnancy. Women with at least moderate symptoms of anxiety and/or depression are either randomised to the intervention group in which they receive 10-14 sessions of CBT, or to the control group in which they receive care as usual. Figure 1 shows the detailed design of the study.

Study outcome measures

The primary outcome in this project is the total emotional and behavioural problems score of the child according to the Child Behaviour Check List 1.5 – 5 (CBCL 1.5-5) at 18 months of age.

Secondary outcomes are the child's mental and psychomotor development at 18 months of age, the change in depressive and anxious symptoms in the mother, obstetric variables such as birth weight, gestational age and Apgar score, the socio-demographic and lifestyle factors, such as alcohol use, smoking and education, and cost-effectiveness of the therapy.

Sample size

Studies on the prevention of mental disorders tend to suffer from problems of insufficient statistical power.[192] In the current study we aimed to get around this problem by using a continuous primary outcome measure and by including a high risk group, i.e. selective prevention.

We decided that effect sizes of 0.35 (midpoint of small – medium effect size) or over on the total problems scale of CBCL 1.5-5 are to be detected. With alpha 5% and power (1-beta) 80%, we have to include 260 participants in our analyses. To account for some drop out we aim at 300 women entering the trial. If 50% eventually meets all criteria and gives informed consent, 600 screen-positives must be identified. The 50% rate is based on studies with psychological interventions during pregnancy aimed at reducing the occurrence of postnatal depression.[191] Given the figures in the literature[1,95] we can expect amply 10% screen-positives on either the anxiety or depression screener. With an estimated 50% comorbidity between anxiety

and depression this means that approximately 15% are eligible for the randomisation. Therefore, 4,000 women needed to be screened. Assuming a response rate of 75% this implicates that 5,333 women must be offered screening.[193] To be on the safe side, we aimed at screening 6,000 women. During the trial it appeared that only 25% rather than 50% of all screen-positive women meets all criteria and gives informed consent. Therefore, we adjusted the number needed to screen for including 300 women to approximately 12,000.

Inclusion

Women in obstetric care in the Netherlands with a significant level of anxiety (6 item STAI ≥42) or at least moderate depressive symptoms (EPDS ≥12) in their first trimester were invited to participate in the trial.

Exclusion

Women fulfilling one or more of the following criteria are excluded:

1. Multiple pregnancy. We decided to exclude women with multiple pregnancy as they have a markedly increased obstetric risk; their inclusion would threaten the homogeneity of the study population and thereby decrease the sensitivity to detect effects.
2. High suicidal risk according to the suicidality subscale score on the MINI International Neuropsychiatric Interview (MINI, defined as a positive response on the question on concrete suicide plans)
3. Presently receiving psychotherapy
4. Substantial physical disease or illegal substance abuse
5. No mastery of the Dutch language
6. A psychiatric history on bipolar disorder, psychoses and manic disorder
7. History of in vitro fertilization

Due to a lower than expected response rate after commencement of the trial we decided to also include participants in hospitals to increase the eligible study population, as opposed to only including participants in primary care. This implied that we decided to no longer exclude multiple pregnancies and women with a history of in vitro fertilization.

Assessments

Participating women are asked to fill out questionnaires until their child is 1.5 years. This is done at eight time points: the screener at baseline (T0), the additional baseline information (T1), and follow-up questionnaires at 24 weeks of gestation (T2), 36 weeks of gestation (T3), at 6 weeks postpartum (T4), 3 months postpartum (T5), 6 months postpartum (T6), 12 months postpartum (T7) and 18 months postpartum (T8). At each time point, the levels of anxiety and depression are monitored by the STAI and the EPDS. As depicted in figure 2, all other questionnaires are filled out once or at several time points.

For anxiety, we use the Dutch version of the 6-item State Trait Anxiety Inventory (STAI). This self-report questionnaire is as valid as the full 20-item version and has frequently been used to measure antenatal anxiety.[95] For the screening on depression we use the Edinburgh Postnatal Depression Scale (EPDS), which has 10 items.[112] This is the most frequently used self-report depression screener in the postnatal period as well as during pregnancy and has been found particularly valid during pregnancy because this scale omits somatic symptoms.[193]

The following information is obtained from participants. The exact time of administration of the corresponding instrument can be found in figure 2.

- Life events before pregnancy are assessed at baseline, using the Negative Life Events Questionnaire (NLEQ).[194]
- Perceived social support is measured according to the 9-item Social Support Questionnaire (SSQ)-short form.[195]
- General health, socioeconomic position, ethnicity, smoking behaviour, alcohol use, psychiatric history (whether the participant has had depression and/or anxiety symptoms before, whether she was treated for this and whether she is presently in treatment for these symptoms is assessed. Socioeconomic position is measured using five indicators: family income, educational level (father and mother), and occupational level (father and mother). This questionnaire is based on a questionnaire used in the Utrecht Health Project (Dutch acronym LRGP: Leidsche Rijn Gezondheids Project, www.lrgp.nl). General health status will also be taken into account according to the EQ-5D.[196]
- Personality is assessed using the NEO Five Factor Inventory (NEO-FFI). The NEO-FFI is a shortened version of the NEO-PR-I and covers the Big Five of personality (neuroticism, extraversion, openness, altruism and conscientiousness).[65] These aspects each contain 6 subscales. The NEO-FFI contains 60 questions, 2 on each subscale. The present study will add 4 full subscales to the short version; two subscales of neuroticism, one of extraversion and one of conscientiousness. This is because we expect them to have the strongest association with persistence of depression and/or anxiety. The NEO-FFI is translated and validated in Dutch.[133]
- Information on previous pregnancies, family size and composition, pregnancy related life events and on reactions on becoming a parent is gathered using questionnaires from the ALSPAC study (www.bristol.ac.uk/alspac).
- Suicide risk is measured using six screening questions from the MINI International Neuropsychiatric Interview.[197]
- Maternal attachment style is measured according to the ECR,[198] which has been translated and validated for the Netherlands by Conradi et al.[199]
- Health care consumption is assessed based on the TIC-P.[200] This instrument allows reliable recall over the past 6 months.[201]
- Coping style is assessed using the Utrechtse Coping Lijst, the UCL.[202]
- A Dutch version of the Dysfunctional Attitude Scale (DAS) is used to measure cognitions and attitudes.[203]

- Obstetric variables such as gestational age, birth weight, Apgar score, complications such as (pre)eclampsia or HELLP, which is obtained from midwives. Women are asked to give consent for this.
- Finally, we use the SCID-II to screen for a possible clinical depressive or anxiety disorder.[204] The SCID-II is the only questionnaire used that has to be taken in a personal interview.

Besides questionnaires for the mother during her pregnancy and the first 1.5 years postpartum, there are assessments of the child at 1.5 years of age.

One of the assessments concerns the Bayley Scale of Infant Development (BSID-III).[205] This is a formal neuropsychological tool to assess the developmental level of a child between 1 and 42 months. It is individually administered by one of the researchers and consists of 3 subscales: cognitive development (mental development index), gross and fine motor development. This tool is widely used in both research and clinical settings and is considered the best and most applied method for the assessment of the child's development to date.[206] Importantly, the instrument has shown to be sensitive. In the context of the present study, maternal anxiety in pregnancy explained as much as 11% of the variance in the Bayley scores in a study among two-year-old toddlers by LaPlante et al.[207]

The second assessment is the Child Behaviour Check List 1.5 – 5 (CBCL 1.5-5) including the Caregiver-Teacher Report form (C-TRF).[208] This well established, reliable and valid scale designed for parents and caregivers comprises seven syndrome scales: emotionally reactive, anxious depressed, somatic complaints, withdrawn, sleep problems, attention problems and aggressive problems. In addition, it contains scales for internalising, externalising and total problems. Symptom scores may further be related to formal DSM-diagnostic criteria.
For the assessment of psychopathology in preschool children it is essential to obtain information from different sources.[209] Therefore we decided to include the C-TRF for the caregivers of the children other than their parents. Parents are asked to hand these lists to the actual caregivers of their children, e.g. grandparents, baby-sitters, kindergarten-coaches, et cetera. Relevant in this respect, a recent review underlined the significance of both the developmental aspects (e.g. as measured with the BSID III) and the infant caregiver relation in the assessment of children 0-3 years of age.[206]

The CBCL has been used successfully in several studies, amongst others on externalizing problems.[207] It has been translated and standardized for use in around 60 countries, including the Netherlands. The CBCL 1.5-5 is considered a sensitive instrument also deployed in several earlier studies.[210,211]

Additional baseline data

Women agreeing to participate are asked to provide additional baseline data at T1, as to find in table 1. About half of these questionnaires are sent to the

participants in print, the other half can be answered online. All follow-up questionnaires are available online. After providing baseline data both in print and online, women are telephoned for the Structured Clinical Interview for DSM-II Disorders (SCID-VI). The SCID-II will allow us to study treatment effects additionally according to diagnostic categories rather than symptom levels.

Randomisation

Right after the SCID-II interview, women are randomised 1:1 to either CBT or CAU. We will create randomisation lists, stratified for parity and socio-economic position, with randomly permuted blocks of random size. Women randomised to the CAU arm are informed about being at risk of depression or anxiety disorder by the researchers and are advised to contact their GP. A close record is kept of all care provided in the CAU arm.

CBT Intervention

The intervention consists of 10-14 individual sessions: 6-10 sessions during pregnancy and 4-8 sessions after delivery (once a week). The CBT is conducted by registered psychologists, specialized in conducting CBT.
CBT posits that an individual's biased information processing leads to maladaptive feelings and behaviours which can culminate in psychological distress and eventually in psychiatric disorders. The main focus of the proposed intervention is targeted on identifying and changing dysfunctional cognitions and schemata (attitudes) specifically for pregnant depressed and anxious patients. In CBT, the Socratic dialog is used aiming to change these dysfunctional cognitions and attitudes permanently. CBT may therefore result in long term protection against psychosocial problems. It is therefore not surprising that cognitive therapy during the acute phase of depression also appears to be effective in reducing subsequent recurrence rates.[84]

The first session will focus on the rationale CBT, i.e. the influence of (irrational or dysfunctional) cognitions and attitudes on feelings and behaviours. Additionally, goal setting is initiated. These therapy goals are unique for each patient. The subsequent sessions are targeted at identifying and amending irrational cognitions and attitudes related to pregnancy, delivery, concerns about the (unborn) child and the future family situation. Each session will address specific pregnancy-related cognitions. Additionally, patients are taught how dysfunctional cognitions and attitudes affect adversely feelings and behaviours.

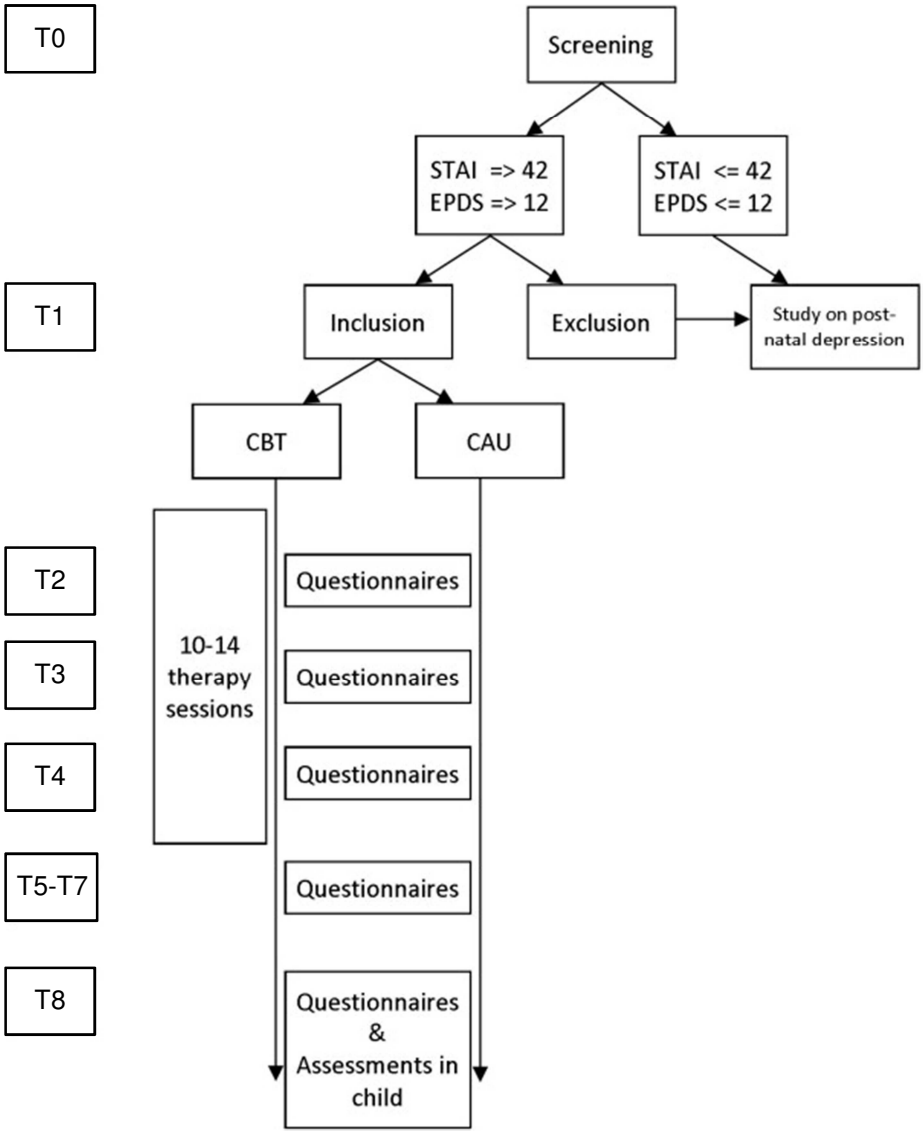
These dysfunctional cognitions and attitudes are challenged and replaced by functional cognitions and attitudes. After each session, patients are given home work. For example, patients are asked to register negative experiences, and accompanying cognitions, feelings and behaviours. Finally, in the last two to four sessions, the newly learned cognitions and attitudes are consolidated.

Table 1: Assessments per measurement

	T0	T1	T2	T3	T4	T5	T6	T7	T8
Depression (EPDS)	X	X	X	X	X	X	X	X	X
Anxiety (STAI)	X	X	X	X	X	X	X	X	X
Personality (NEO-FFI)		X		X		X			
Life events before pregnancy (NLEQ)		X							
Life events during pregnancy		X		X		X			
Perceived social support (SSQ)		X							
Coping styles (UCL)		X	X	X	X				
Attitudes (DAS)		X	X	X	X				
Maternal attachment (ECR)		X						X	
Quality of life (EQ-5D)		X	X	X	X	X		X	
Sociodemographic/-economic factors		X							
Lifestyle		X		X		X			
Breastfeeding						X			
General health		X							
Health care consumption		X			X	X		X	X
Previous pregnancies		X							
Suicidality (MINI)		X							
Clinical Diagnostic Interview (SCID-II)		X							
Child Behaviour (CBCL)									X

Measurements in the PROMISES-study: The screener at baseline (T0), the additional baseline information (T1), and follow-up questionnaires at 24 and 36 weeks of gestation (T2 and T3), and at 6 weeks (T4), 3, 6, 12, and 18 months postpartum (T5 – T8).

Figure 1: Flow diagram



Data analysis

If necessary, skewed continuous variables will be transformed to normality prior to the analyses. The primary outcome, i.e. the CBCL scores at month 18, will be compared between the treatment arms using the unpaired t-test. This test will also be used for detecting differences in the Bayley scores by month 18 and the obstetric variables measured at birth. The latter group of variables will be tested using the Chi2 test if categorical. Differences in attachment style at month 12 will be analyzed using analysis of covariance with the baseline variable as a covariate. Continuous outcomes that were measured more than twice (e.g. EPDS and STAI) will be analyzed as dependent variables using linear mixed models for fixed and random effects. These models are superior for the analysis of longitudinally correlated data and can optimally deal with missing values.[212] A mixed model ascribes a unique intercept and slope estimate to each individual, while making use of information across individuals for predicting these quantities. In these analyses, a treatment*time variable indicating the effect of the intervention will be included as an independent variable. If despite randomisation important baseline differences exist in prognostically important variables such as the extent of social support or history of life events, they will be adjusted for. Additional analyses will be conducted to demonstrate mediation of the effect of CBT on the child's outcomes by maternal symptom level, alcohol or nicotine consumption in pregnancy, medication use or perinatal outcomes.

The analyses will primarily be carried out according to the intention-to-treat (ITT) principle, i.e. the participants will be analyzed according to their randomised allocation, regardless of the actual CBT undergone, or time in study after baseline. Aside from the optimal validity of ITT analyses, they quantify the effects on the outcome measures that would be obtained in practice. The magnitude of the effect measured in an ITT analysis incorporates the effects caused by non-adherence to CBT, behavioural changes, et cetera. Secondary analyses will be of the 'per protocol' type meaning that they will be restricted to those women that had all of the CBT sessions.

Considering specific target populations, there is evidence that the socio-economically deprived may have more benefit from treatment of depression during pregnancy.[24] Therefore, subgroup analyses will be undertaken according to socio-economic position. Subgroup analyses will also be undertaken according to parity.
Differences in effect of CBT between subgroups will be statistically evaluated by testing treatment by subgroup interaction terms. Effect parameters will be supplied with a 95% confidence interval.

Economic evaluation

An economic evaluation will be conducted alongside the trial to assess the cost-effectiveness of CBT compared to care as usual in the current study population. Information on costs and health outcomes will be prospectively collected during 24 months (starting at baseline until 18 months after birth) for both mother and child. Two complementary economic analyses will be conducted. The primary outcome measure of the planned cost-effectiveness analysis is the total emotional and behavioural problems score of the child according to the CBCL at 18 months of age.
In the additionally planned cost-utility analysis, QALYs (Quality Adjusted Life Years) will be used as the primary outcome measure. The study will be performed from a societal perspective. Medical costs that will be assessed include costs related to CBT, contacts with healthcare professionals, and medication use. Outside the healthcare sector, costs of informal care and productivity losses will be taken into account. Unit prices will largely be based on Dutch standard prices in order to facilitate comparisons with other economic evaluations. Cost-effectiveness acceptability curves will be used to inform decision-makers on the probability that the studied intervention is cost-effective.

This study protocol was approved by the medical ethical committee of the University Medical Center Groningen.

CHAPTER 8

Cognitive behavioural therapy for treatment of anxiety and depressive symptoms in pregnancy: a randomised controlled trial

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Abstract

Background

Anxiety and depressive symptoms during pregnancy are associated with adverse maternal and child outcomes. Available evidence on the effectiveness of cognitive behavioural therapy (CBT) during pregnancy for treatment of these symptoms is limited and inconclusive. The aim of the present study was to investigate the effect of individual CBT on anxiety and depressive symptoms during pregnancy, as compared to care as usual (CAU), using an RCT design and including pregnant women with subclinical anxiety and/or depressive symptoms or disorders.

Methods

Pregnant women were screened in midwife practices or hospitals throughout The Netherlands and those with at least moderate anxiety and/or depressive symptoms in their first trimester were invited. Participants in the intervention group received 10-14 CBT sessions, of which 6-10 during pregnancy. The present analysis shows results from a secondary outcome measure: anxiety and depressive symptoms at 36 weeks of gestation as measured by the STAI and EPDS, respectively.

Results

Out of the 1007 women who were invited, 282 gave informed consent. The analysis included 140 participants in the CBT arm and 142 in the CAU arm. Fifty-five percent of our sample had anxiety and/or depressive DSM-IV disorders. Results show that levels of anxiety and depressive symptoms decrease during pregnancy ($p<0.001$ and $p<0.05$, resp.). However, no differences in scores were observed between the CBT and CAU groups: difference in mean STAI score: -1.4 (95%CI -4.5;1.7), difference in mean EPDS score: -1.1 (95%CI -2.2;0.1). Stratified analyses according to socio-economic position, parity, severity of symptoms, and DSM-IV disorder do not show statistical significant effect sizes.

Conclusions

The present study found no evidence of a beneficial effect of CBT treatment for anxiety and depressive symptoms during pregnancy, when compared to CAU. More evidence needs to be gained for which specific groups screening and treatment may be beneficial during pregnancy, including especially pregnant women with anxiety and/or depressive disorders.

Background

It is estimated that 10-20% of all pregnant women suffer from symptoms of anxiety and depression during pregnancy.[1,2,213,214] These symptoms may adversely affect both maternal and child health outcomes. For the mother, there seems to be an increased risk for developing postpartum depression.[215,216] As for the child, it has been suggested that, in line with Barker's "foetal origins of adult disease"-hypothesis, an adverse mental state of the mother during pregnancy may be an important and modifiable risk factor for psychosocial problems in her children.[21,217] Previous research suggests that anxiety and depression during pregnancy may affect the maternal stress system, possibly leading to an overexposure to glucocorticoid levels in the foetus, which subsequently may influence its development.[218,219] Early identification and treatment of anxiety and depression during pregnancy may therefore help to prevent adverse maternal and child outcomes.

Moderate to severe depression among adults is commonly treated with antidepressants.[220] However, during pregnancy, women prefer psychological treatment,[83] mainly because the safety of medication to treat anxiety and depression during pregnancy cannot be guaranteed.[79,221] Cognitive behavioural therapy (CBT) has been shown to be effective in treating anxiety and depression in the general population.[85,86] Present NICE guidelines suggest CBT for treatment of anxiety and depression also during pregnancy.[74] However, evidence for the effectiveness of CBT during pregnancy is sparse. We are aware of only three randomised controlled trials (RCTs) that investigated the effect of CBT on depressive symptoms during pregnancy. Out of these, only one study also investigated the effect of CBT on anxiety symptoms during pregnancy. Women who were included in the latter study (n=277) reported a prior history of depression, or scored >10 on the Edinburgh Postnatal Depression Score and/or >23 on the Antenatal Risk Questionnaire.[82] Results showed no beneficial effect of six weekly CBT sessions on levels of anxiety nor on levels of depression, when compared to the control condition that included an information booklet.[82] In the pilot RCT, conducted by Burns and colleagues, participants meeting the ICD-10 criteria on the Clinical Interview Schedule for depression, received up to 12 CBT sessions (n=36).[80] Although not statistically significant, the intervention group showed a greater reduction in depression rates compared to the control group that received care as usual.[80] Lastly, the study by Le and colleagues (n=217) included Latina women who scored ≥16 on the Centre for Epidemiological Studies Depression Scale and/or reported a prior or family history of depression, but who did not meet a current diagnosis of depression.[81] A statistical significant greater reduction of depressive symptoms during pregnancy was found in the intervention group, that received eight weekly CBT sessions, when compared to the control condition that included care as usual.[81] Given these contradictory findings, more

evidence is needed on the effectiveness of CBT when treating anxiety and depression during pregnancy, and for whom CBT may be most beneficial.

The aim of the present study was to investigate the effect of individual CBT on maternal mental health during pregnancy, as compared to care as usual (CAU), using a RCT design and including pregnant women with subclinical anxiety and/or depressive symptoms or disorders. In the CBT arm, we expected a (greater) reduction of anxiety and depressive symptoms during pregnancy, when compared to CAU.

Methods

Setting and participants

The present study used data from the 'Pregnancy Outcomes after a Maternity Intervention for Stressful EmotionS' (PROMISES) trial. This single-blind-RCT investigated the effects of CBT compared to CAU in pregnant women with symptoms of anxiety and depression on maternal symptom levels during and after pregnancy, obstetric outcomes and the child's development including behavioural and emotional problems. A detailed description of the PROMISES trial can be found elsewhere.[222]

Due to a lower than expected response rate after commencement of the trial we decided to also include participants in hospitals to increase the eligible study population, as opposed to only including participants in primary care. This implied that we decided to no longer exclude multiple pregnancies and women with a history of in vitro fertilization. Obstetric healthcare in The Netherlands is organized as follows. Approximately 85%, of all pregnant women with low-risk pregnancies typically enter primary care and are monitored by independent midwives.[223] The remaining 15% is referred to a gynaecologist/obstetrician in a hospital.[223] All women visiting the participating midwifery practices (n=109) and obstetrics and gynaecology departments of hospitals (n=9) throughout the Netherlands were invited to participate in the Pregnancy Anxiety and Depression study (PAD). This prospective cohort study investigated psychological, social and medical factors during and after pregnancy.[110] Women were screened for anxiety and depressive symptoms in their first trimester of pregnancy (T0). Women with at least moderate levels of anxiety and/or depressive symptoms and who indicated to be interested in a follow-up study, were invited to participate in the PROMISES trial. Women fulfilling one or more of the following criteria were excluded from participation in the PROMISES trial:

1. High suicidal risk according to the suicidality subscale score on the MINI International Neuropsychiatric Interview [197]
2. Presently receiving psychotherapy
3. Substantial physical disease or illegal substance abuse
4. No mastery of the Dutch language

5. Having a psychiatric history on bipolar disorder, psychoses and manic disorder

Women who provided written informed consent were asked to fill out online questionnaires both during and after pregnancy. The present study used data collected on the following occasions: screening (T0), baseline information at 19 weeks gestational age (GA) (T1) and follow-up questionnaires at 36 weeks GA (T2). Measures used for the present analysis, and their corresponding time points, can be found in table 1.

Assessments

The level of anxiety was monitored using the Dutch version of the validated 6-item State Trait Anxiety Inventory (STAI), which has also been used to measure anxiety symptoms during pregnancy.[95] Depressive symptoms were measured using the Dutch version of the validated 10-item Edinburgh Postnatal Depression Scale (EPDS).[112] The following cut-off values were used: STAI>42 and EPDS≥12). Socio-demographic factors that were measured include questions about socio-economic status (SES), age, and parity. SES was assessed using three indicators: family income and educational level of both the father and mother. These indicators were weighted and categorized as low SES, middle SES, and high SES. Questions about SES were based on a questionnaire used in the Utrecht Health Project (Dutch acronym LRGP: Leidsche Rijn Gezondheids Project, http://www.zorggegevens.nl.zorg/eerstelijnszorg/leidsche-rijn-gezondheidsproject/). Finally, the anxiety and mood disorder section of the Structured Clinical Interview for DSM-VI Disorders (SCID-II) was used to assess the presence of an anxiety or depressive disorder.[204]

Table 1: Assessments per time point

	T0 (screening)	**T1 (20 wks GA)**	**T2 (36 wks GA)**
Anxiety symptoms (STAI)	x	x	x
Depression symptoms (EPDS)	x	x	x
Sociodemographic & -economic factors		x	
Suicidality (MINI)		x	
Clinical Diagnostic Interview (SCID-II)		x	

STAI= State Trait Anxiety Inventory
MINI= MINI international neuropsychiatric Interview
SCID-II= Structured Clinical Interview for DSM-IV disorders
GA= Gestational Age

Power calculation

In total 282 were included in the PROMISES study. Given this sample size, an equal allocation rate, and based on an independent samples t-test (5% significance level, two-sided), we were able to detect at least an effect size of 0.34 or over with 80% power. We considered this to be a relevant effect size, given that previous studies among the general (patient) population indicated an effect size of around 0.4 or higher for anxiety and depression treatment.[85,86]

Randomisation

Eligible women were randomised right after baseline assessments, including the SCID-II interview, 1:1 to either CBT or CAU by an independent research assistant. To this end, a computer-generated randomisation list was used, stratified for parity and socio-economic position, with randomly permuted blocks of random size.

CBT Intervention

CBT trained psychologists throughout the Netherlands (n=31), and who are BIG registered, delivered the intervention. All psychologists received additional specific two-day training by a board certified clinical psychologist (CLHB). During this training all components of the intervention were explained and there was room for practice. The treatment protocol was developed by CLHB and consisted of 10-14 weekly individual sessions, of which 6-10 were scheduled to be delivered during pregnancy. The treatment encompassed several optional modules with specific evidence-based CBT interventions focusing on the treatment of anxiety disorders, depressive disorders, or trauma and post-traumatic stress disorder. In addition, the overall focus of the treatment was targeted at identifying and changing dysfunctional cognitions, and beliefs. Each session addressed pregnancy-related cognitions and attitudes. Moreover, all sessions were structured with homework assignments, and discussion of these assignments, and the rationale of each session was explained. A treatment manual is available on request. During the period of the trial, regular supervision was given by CLHB and treatment integrity was checked by organizing supervision sessions.

Control group

The control group received CAU, which was an advice to contact their general practitioner and/or midwife because of an increased risk of developing an anxiety or depressive disorder. In view of the pragmatic

nature of the trial, no restrictions were imposed on treatments in the CAU group.

Outcome

The primary outcomes of the present study were the level of anxiety and depressive symptoms at 36 weeks GA. Secondary outcomes included a measure of distress, 'distress score', as indexed by the equally weighted standardized means of the STAI and EPDS scores.

Statistical analyses

Characteristics of the study participants were described according to randomised group using appropriate descriptive analyses. STAI, EPDS, and distress scores at 36 weeks GA were analysed as continuous dependent variables using linear regression with STAI, EPDS, and distress scores at T0 as independent variables, next to the randomised group variable. This analysis of covariance approach is favoured, because it accounts for baseline imbalance across groups and generally has superior statistical power to detect intervention effects when compared to other approaches, such as change scores.[224] In each analysis, the stratification variables parity and SES were added as covariates. Primarily, the analyses were carried out according to the intention-to-treat principle. Secondary analyses were 'per protocol', i.e. restricted to those participants who had a minimum of 6 sessions.

Predefined subgroup analyses within the primary outcome analyses were undertaken according to socio-economic status (low vs. middle vs. high) and parity (primiparae vs. multiparae). In addition, severity of anxiety and depressive symptoms (below vs. above cut-off values of 42 for STAI and 12 for EPDS) and the presence of an anxiety and/or depressive disorder according to DSM-IV were studied as subgroup analyses. Balance between the CBT and CAU groups was checked for age and present DSM-IV diagnosis, and analyses were additionally adjusted for these variables when appropriate. Differences in effect of CBT between subgroups were evaluated by statistically testing the significance of treatment X subgroup interaction terms. Effect parameters were supplied with a 95% confidence interval (95%CI). As a sensitivity analysis we studied the influence of missing data on all results. The percentage missing data ranged from 0 to 28.7 (depressive symptoms at 36 weeks GA) for the variables of main interest.

We used multiple imputation by chained equations under the assumption that the missingness mechanism is missing at random or missing completely at random. We imputed 20 datasets and data were pooled using Rubin's rules.[101] The imputation model included all variables of interest that may predict missingness in the primary outcome. We studied the missing data

mechanism of the primary outcome variables by predicting missingness (yes/no) of each of these variables using a multivariable logistic regression analysis. All variables that were considered potential predictors of missingness were entered as independent variables. These analyses showed an explained variance of 35.3% for anxiety symptoms and 36.5% for depression symptoms (Nagelkerke's R^2). This suggested that data were missing at random at least to some extent, but data being missing not at random can never be excluded. The level of statistical significance was set at 0.05, two-sided. All analyses were performed using IBM SPSS Statistics version 20.0.

Ethics

The PROMISES trial has been approved by the medical ethical committee of the University Medical Center Groningen.

Results

Descriptives

Following the screening of 8143 pregnant women, a total of 1248 women (15%) experienced at least moderate symptoms of anxiety and/or depression, of which 241 women were excluded. The remaining 1007 women were invited to participate in the PROMISES trial of which 282 women (28%) decided to participate, 140 in the CBT group and 142 in the CAU group (figure 1). In the CBT group, 15 participants refused to start the intervention for various reasons, including no time or expecting that the treatment would be too burdensome. Participants who started the treatment had a mean of 9 sessions (range 1-15) and 94 participants completed at least six sessions. Thirty-one participants did not complete the number of scheduled sessions for various reasons (e.g. not presenting with symptoms anymore, no time, pregnancy complications).

Characteristics of the participants are shown in table 2, according to randomisation status. Both groups were comparable on all variables, although participants in the CBT group more often presented with an anxiety or depression diagnosis and participants in the CAU group more often with a comorbid diagnosis (p=0.07).

Therapy integrity

All psychologists successfully finished the specific training for the treatment under study. Four supervision sessions have been organized for which all psychologists were invited for participation. All psychologists except four attended at least one session while treating a participant. Content of the discussions in the supervision sessions did not give rise to believe that treatment was given otherwise than intended. Allocation of participants receiving CBT was based on location and availability of the psychologists.

Intention to treat analyses

Table 3 and 4 show the mean STAI and EPDS scores at 36 weeks GA and the mean differences between the CBT and CAU groups. Compared to STAI and EPDS scores at screening (T0), both the CBT and CAU groups showed a decrease in anxiety and depressive symptoms ($p<0.001$ and $p<0.05$, respectively). Participants in the CBT group showed slightly higher STAI and EPDS scores at 36 weeks GA compared to the CAU group but differences were not statistically significant. Furthermore, no differences in the distress score were observed between groups (table 5). After multiple imputation, estimates attenuated somewhat for STAI and EPDS scores at 36 weeks GA, when compared to estimates from complete case analyses (table 3 to 5).

Per protocol analyses

Ninety-four participants received 6 or more sessions and thus were included in the per protocol analyses. Groups were unbalanced for the variables age (p=0.04) and present diagnosis (p=0.03), therefore analyses were adjusted for these variables. There was no evidence of a beneficial effect of the intervention (p>0.05). Estimates after multiple imputation were not notably different when compared to the estimates from complete case analyses (table 3 to 5).

Subgroup analyses

Compared to the overall effectiveness estimates, the analyses in subgroups of SES, parity and scoring above cut-off value of STAI or EPDS showed no substantial differences in effect size. In the subgroup of participants with a low SES participants in the CBT group showed notably higher EPDS scores at 36 weeks GA, compared to the CAU group (β=-2.7, 95%CI -4.9;-0.5), although the interaction term was not statistically significant (p=0.13). In the imputed analyses this finding attenuated (β=-1.3, 95%CI -3.2;0.6). Other subgroup analyses on present DSM-IV diagnosis did not show substantial differences in effect size (table 3 to 5).

Comparison with sample that declined to participate

We compared participants in the PROMISES trial with women who declined participation, but were still included in the PAD study, on the variables anxiety and depression at time of screening (T0) and at 36 weeks GA. We found that participants in the PROMISES trial had slightly higher levels of anxiety (p>0.05) and significantly higher levels of depression at T0 (p=0.02), compared to women who declined participation. Furthermore, in the group of women who declined participation, both anxiety and depressive symptoms decreased by 36 weeks GA. For depressive symptoms, this decrease was even higher when compared to the PROMISES participants (p=0.04).

Figure 1: Trial profile

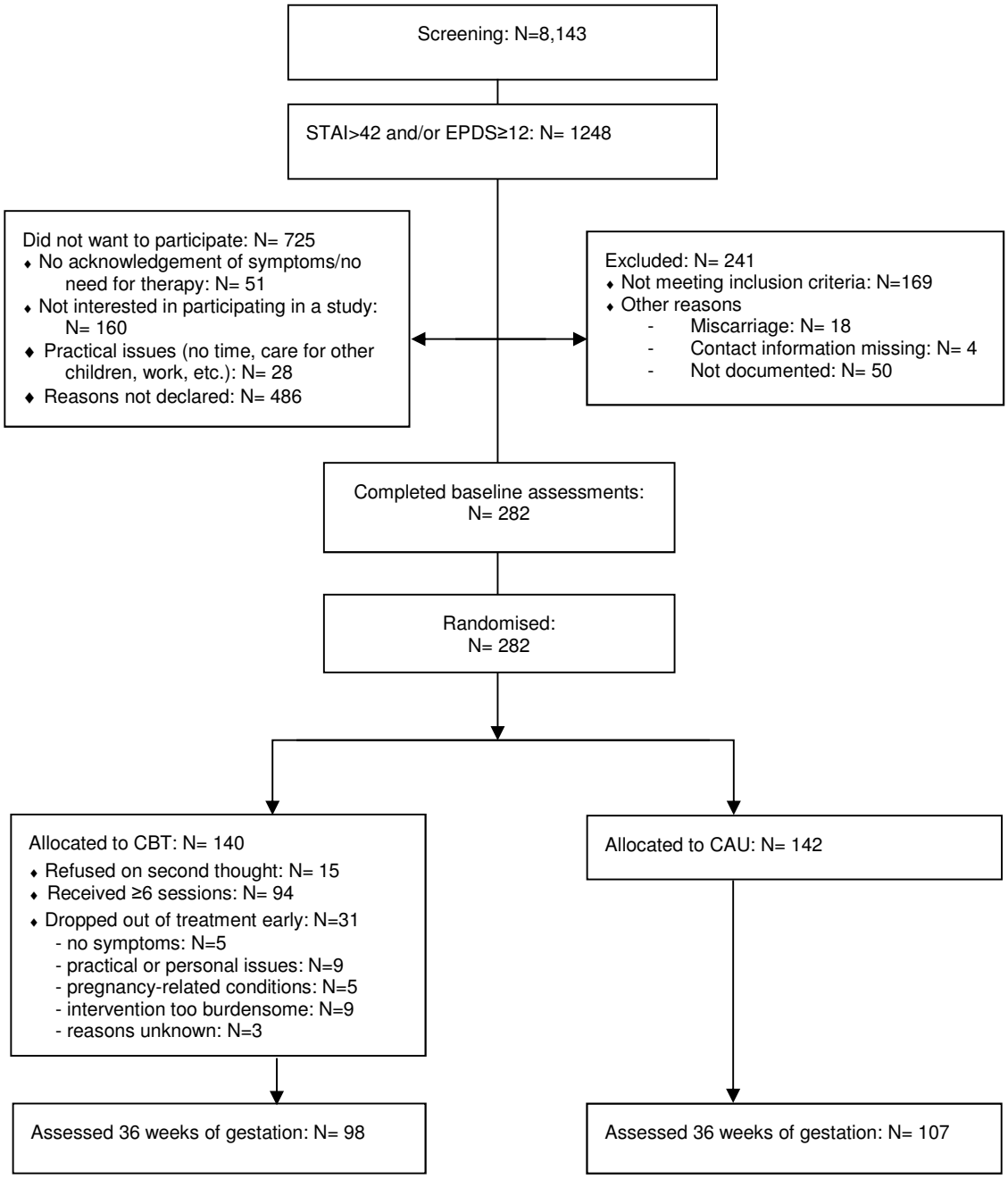

Table 2: Characteristics of the randomised study participants

	Intervention (N=140)	**Care as usual (N=142)**
	Mean (SD)	***Mean (SD)***
Age in years	34.8 (4.6)	33.7 (4.5)
STAI-score screening (To)	49.7 (7.8)	49.3 (7.5)
EPDS-score screening (To)	10.1 (4.2)	10.1 (4.1)
Zscore Distress-score screening (To)	0.6 (1.5)	0.4 (1.4)
	N (%)	***N (%)***
Multipara	70 (50.0)	73 (51.4)
Socio-economic status		
Low	48 (34.3)	51 (35.9)
Moderate	36 (25.7)	35 (24.6)
High	56 (40.0)	56 (39.4)
Present diagnosis (DSM-IV)		
Anxiety	57 (40.7)	41 (28.9)
Depression	14 (10.0)	9 (6.3)
Anxiety and depression	14 (10.0)	20 (14.1)
Previous diagnosis (DSM-IV)		
Anxiety	14 (10.0)	9 (6.3)
Depression	58 (41.4)	63 (44.4)
Anxiety and depression	10 (7.1)	14 (9.9)

STAI= State Trait Anxiety Inventory
EPDS= Edinburgh Postnatal Depression Score
DSM-IV= Diagnostic and Statistical Manual of Mental Disorders 4th edition
¥ Panic disorder was only present among participants with more than one anxiety disorder

Table 3: Anxiety symptom scores at 36 weeks GA. Values are differences in means (95% CI) unless stated otherwise (complete case analyses).

	Intervention (N=140)	**Care as usual (N=142)**
STAI score, mean (SD)	43.2 (10.6)	41.5 (12.6)
Intention to treat (N=205)	-1.4 (-4.5;1.7)	
MICE	-0.3 (-3.7;3.0)	
Subgroups		
Anxiety and/or depressive disorder (N=113)	-1.3 (-5.8;3.2)	
Anxiety diagnosis (N=76)	-3.5 (-8.7;1.6)	
*Comorbid diagnosis (N=19)**	4.8 (-8.0;17.6)	
Above cut-off STAI (N=193)	-1.5 (-4.7;1.8)	
Per protocol† (N=186)	0.8 (-2.6;4.1)	
MICE†	-0.2 (-3.7;3.4)	
Data missing, N (%)	42 (30.0)	35 (24.6)

Table 4: Depressive symptom scores at 36 weeks GA. Values are differences in means (95% CI) unless stated otherwise (complete case analyses).

	Intervention (N=140)	**Care as usual (N=142)**
EPDS score, mean (SD)	9.4 (4.6)	8.2 (4.7)
Intention to treat (N=200)	-1.1 (-2.2;0.1)	
MICE	-0.4 (-1.5;0.8)	
Subgroups		
Anxiety and/or depressive diagnosis (N=109)	-1.2 (-3.0;0.5)	
Depression diagnosis (N=18)	-2.2 (-8.8;4.4)	
*Comorbid diagnosis (N=19)**	0.9 (-4.6;6.5)	
Above cut-off EPDS (N=69)	-0.7 (-3.0;1.7)	
Per protocol† (N=180)	0 (-1.3;1.2)	
MICE†	-0.2 (-1.3;1.0)	
Data missing, N (%)	43 (30.7)	39 (27.5)

Table 5: Distress scores at 36 weeks GA. Values are differences in standardized means (95% CI) and Log transformed, unless stated otherwise (complete case analyses).

	Intervention (N=140)	**Care as usual (N=142)**
Z score distress score, mean (SD)	0.6 (0.9)	0.9 (1.4)
Intention to treat (N=196)	0.1 (-0.2;0.4)	
MICE	0.1 (-0.2;0.3)	
Subgroups		
Anxiety and/or depression diagnosis (N=108)	0.1 (-0.4;0.5)	
Per protocol† (N=177)	0 (-0.3;0.3)	
MICE†	0 (-0.3;0.3)	
Data missing, N (%)	45 (32.1)	41 (28.9)

Differences between groups are studied using linear regression and are adjusted for STAI (table 3)/EPDS (table 4)/distress (table 5) scores at To, parity and SES

** adjusted for age*
† adjusted for present DSM-IV diagnosis according to SCID-II and age

MICE= multiple imputation by chained equations
STAI= State Trait Anxiety Inventory, used cut-off value >42
EPDS= Edinburgh Postnatal Depression Score, used cut-off value ≥12

Discussion

The present study investigated the effect of CBT compared to CAU, in pregnant women presenting with at least moderate levels of anxiety and/or depressive symptoms during the first trimester. Although levels of anxiety and depressive symptoms decreased during pregnancy, we found no evidence that receiving CBT reduced anxiety and depressive symptoms during pregnancy more than CAU.

Comparison with other studies and explanation of findings

Our results are surprising in that there is ample evidence that CBT is effective in treating anxiety and depression outside pregnancy. Nevertheless, our findings are in line with a study by Austin and colleagues (n=277) that also included a sample of women with subclinical symptoms or anxiety and depressive disorders. The authors found no beneficial effect of CBT on both anxiety and depressive symptoms during pregnancy.[75] They suggested that the control condition, i.e. an information booklet including strategies to prevent and handle postnatal distress, can be considered as an equal form of psychosocial support.[75] In contrast, the study by Le et al (n=217) found a significant reduction in depressive symptoms as a result of CBT among pregnant women with subclinical symptoms. Yet, this study included a sample of Latina women, and the authors admit that findings are limited in generalizability. Burns and colleagues conducted a small pilot study (n=36) including a home-based CBT intervention and also found a decrease in depressive symptoms as a result of CBT, although this was not statistical significant.[80] In this study among pregnant women with a depressive disorder, EPDS baseline scores were relatively high (median: 16-20) compared to the scores in our sample (mean: 10), thus providing more room for improvement. Furthermore, there is evidence indicating that interventions in a home setting may be especially valuable due to an active involvement with mothers.[225] Moreover, women participating in this study indicated at time of screening that they wanted help themselves, that may have made them more motivated to handle their depressive symptoms. It appears that patient engagement in CBT is a predictor of greater reductions in both anxiety and depressive symptoms.[226]

Interestingly, we found an overall decrease in both anxiety and depressive symptoms, which is in line with previous studies.[80,81,227] There may be several explanations for this overall decrease of symptoms. First, as the study population is selected based on a high score of anxiety and/or depressive symptoms, regression to the mean may have contributed to the overall decrease of symptoms during pregnancy. Second, anxiety and depressive symptoms may be confused with or be the result of other symptoms common in pregnancy, such as hormonal changes or sleep deprivation. Hormonal changes are highest in first trimester, which may partly explain why anxiety

and depressive symptoms decrease during pregnancy.[228] Third, it may be that overall participation in the study (i.e. filling in questionnaires and follow-up) is an intervention per se, having the potential to improve levels of anxiety and depression in both groups.[239] As for the lack of a beneficial effect of CBT in the present study, it should be stressed that our sample was heterogeneous in the sense that we included women with anxiety and depressive disorders (53% of our sample), and the other half consisted of women with subclinical symptoms. Also, overall the mean level of anxiety and depressive symptoms was relatively low. It may be that for the group of women presenting with relatively low levels of anxiety and depressive symptoms, the level of these symptoms cannot decrease much further. Consequently, a beneficial effect of CBT cannot be demonstrated when compared to care as usual. Another explanation of observing no beneficial effect of CBT may be found in underlying biological mechanisms during pregnancy. There is convincing evidence that the HPA-axis functions differently during pregnancy. Cortisol levels increase during pregnancy and the HPA-axis responsiveness to stress may change.[230] These changes in the physiological stress system may be reflected in a diminished appraisal of stress,[231] and possibly explain why decreases in reported anxiety and depressive symptoms are reported. Concurrently, women may be less susceptible to interventions that target anxiety and depression during pregnancy. Finally, it may be argued that we were not able to adequately measure the effect of CBT using self-report measures for anxiety and depression. In a previous RCT study (n=61) by Richter et al., the effect of CBT during pregnancy was studied on perceived stress and salivary cortisol levels.[232] Compared to the control group, women in the intervention group showed a decrease in diurnal cortisol but not in perceived stress. There is more evidence that objective measures, such as cortisol measures, may not correlate with self-report questionnaires.[233,234] Thus, CBT may, despite our findings, still have reduced the activity of the maternal stress system. Obstetric and child outcomes of the present study may shed light on this.

Strengths and limitations

Some strengths of this study should be mentioned. This study is one of the few RCT studies investigating the effect of CBT on anxiety and depression during pregnancy. We included a population-based sample that may allow us to generalize our findings to a larger Dutch pregnant population presenting with anxiety and/or depressive symptoms, as opposed to if we would have recruited a sample from clinical settings only. Furthermore, we used a manualised CBT intervention utilized by trained CBT psychologists to increase reliability. Limitations include the low number of participants in subgroups. As a result, subgroup analyses were underpowered and we were unable to investigate the effect of CBT among participants with various DSM-IV anxiety, depressive, and comorbid disorders. Another limitation comprises the low participation rate of women who were invited to

participate in the trial. Only 30% of the participants in the PAD study presenting with at least moderate anxiety and/or depressive symptoms also agreed to participate in our intervention trial. Our response rate was somewhat low when compared to that of other similar studies that included pregnant women who were not active help-seekers. The study of Austin et al., that included pregnant women with subclinical symptoms or anxiety and depressive disorders, showed a response rate 39%.[82] The study by Le et al. that included women with subclinical symptoms or a previous depression had an even higher response rate of 70%.[81] Also the response rate of a non-CBT RCT, i.e. self-help workbook and telephone support, that was aimed at reducing anxiety and depressive symptoms among pregnant women with and without symptoms was higher than ours, that is 61%.[235] At baseline and 36 weeks of gestation we had some missing data, but the sensitivity analyses suggested that missing data probably did not majorly affect our findings. Finally, we were unable to measure cortisol levels in the present study. Such physiological stress measure could have provided us with more information about the lack of a beneficial effect of CBT during pregnancy that we observed.

Clinical relevance

The clinical significance of treating anxiety and depression during pregnancy using CBT remains unclear. Our study was unable to detect an effect size of 0.34 or above in pregnant women who were not actively help-seeking. We have to be cautious to conclude that CBT is not effective during pregnancy as we could not properly study the effect in women with DSM-IV disorders and other subgroups. We observed for instance a trend showing that lower SES women following CBT had higher EPDS score compared to women receiving CAU. Future research should provide more insight on the effects of CBT during pregnancy among specific groups of pregnant women. Moreover, CBT sessions provided in our study continued after pregnancy, and CBT may show a beneficial effect once treatment is completed. Follow-up assessments after pregnancy may provide more information on this.

Treatment acceptability is important to consider given the relatively low response rate in our study. Following treatment during pregnancy may compete with other factors such as work, care of other children, and pregnancy-related issues (e.g. fatigue). Furthermore, almost half of our study sample consisted of participants with subclinical anxiety and/or depressive symptoms. It may be suggested that for this group of women, at risk for developing a disorder, minimal interventions (e.g. an information booklet, a general practitioner or midwife symptom-focused consult) may be sufficient to treat these symptoms, as opposed to CBT.

Despite the lack of clear evidence, current NICE guidelines suggest CBT as an appropriate treatment option for both anxiety and depression following

the screening for anxiety and depressive symptoms.[74] However, it has been suggested that screening in itself should be part of a process including access to effective treatment.[236] As such, our data suggests that it seems not solid to introduce universal screening for all pregnant women yet. More evidence needs to be gained for which specific groups screening and treatment may be beneficial during pregnancy, including pregnant women with anxiety and/or depressive disorders.

Conclusion and future directions

This study found no evidence for a beneficial effect of CBT treatment for anxiety and depressive symptoms during pregnancy, when compared to CAU. We propose that the lack of a beneficial effect of CBT during pregnancy may be due to our heterogeneous sample including pregnant women with subclinical symptoms and DSM-IV anxiety and/or depressive disorders. Large RCT studies are needed on the treatment of anxiety and depressive symptoms during pregnancy, especially focused on pregnant women with anxiety and/or depressive disorders. Finally, future studies could explore potential underlying biological mechanisms and the effect of CBT during pregnancy on the offspring.

CHAPTER 9

Effects of cognitive behavioural therapy during pregnancy on perinatal outcomes: the PROMISES randomised controlled trial

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Abstract

Background

Antenatal anxiety and depressive symptoms are highly prevalent and have been associated with multiple adverse maternal and perinatal outcomes. Currently, international guidelines recommend that these symptoms are mostly antenatally treated using cognitive behavioural therapy (CBT) because it is commonly believed that CBT during pregnancy, unlike antidepressants, has no adverse effects on perinatal outcomes. However, to date, no previous trials have been published on the effects of CBT during pregnancy on perinatal outcomes.

Methods

We performed a multi-centre, single-blind randomised controlled trial in pregnant women with depressive and/or anxiety symptoms/disorders who visited one of the participating 109 midwifery practices or nine hospitals. We enrolled women with at least moderate symptoms of depression (Edinburgh Postnatal Depression Scale; EPDS≥12) and/or anxiety (State Trait Anxiety Inventory; STAI>42). Participants were randomised (1:1) by computer-generated sequence to receive either primary antenatal CBT or care as usual (CAU), stratified by parity, and socio-economic status. The present analyses assessed major perinatal outcomes on both intention-to-treat and per-protocol. The trial was registered at Trialregister.nl, NTR2242.

Results

Of the 1007 women invited, 282 (28%) were randomised to receive antenatal CBT (n=140) or CAU (n=142) between April 1, 2011, and Sept 1, 2014. No substantial baseline differences were observed. Offspring of participants in the CBT group showed overall a slightly lower birth weight and lower gestational age at delivery compared to the CAU group but differences were not statistically significant. However, in participants with a present DSM-IV anxiety diagnosis (N=98), we found that the mean birth weight was over 275 grams lower (β=-275.4, 95% CI -530.6; -20.2) and that the mean gestational age was approximately a week lower (β=-0.978, 95% CI -1.872; -0.084) in the CBT group than in the CAU group. Results of per-protocol analyses showed somewhat stronger associations and imputation of missing values did not alter the results. No differences in Apgar scores were observed.

Conclusions

Antenatal CBT seems to have a significant negative effect on major perinatal outcomes when provided as treatment of antenatal anxiety during pregnancy. Further research is needed to assess whether the adverse effects of antenatal CBT are lasting.

Research in context

Evidence before this study

We aimed to identify studies on the effects of cognitive behavioural therapy (CBT) during pregnancy on perinatal outcomes. We searched MEDLINE and NCBI up to June 30, 2015, with terms including "pregnancy", "prenatal depression", "perinatal depression", "maternal depression", "maternal depressive symptoms", "prenatal anxiety", "perinatal anxiety", "maternal anxiety", "maternal anxiety symptoms", "maternal mental health", "treatment", "intervention", "cognitive therapy", "cognitive behavio(u)r therapy", "individual psychotherapy", "perinatal outcomes", "parturition", "obstetric outcomes", "birth weight", "gestational age", and "Apgar scores". We did not limit our search by article type or language. While literature provides evidence for an effect of CBT in preventing postpartum depression, none of the studies provided evidence on perinatal effects of antenatal CBT, neither positive nor negative.

Added value of this study

Our study provides evidence from a randomised controlled trial of the effects of antenatally provided cognitive behavioural therapy on major perinatal outcomes. Overall, antenatal CBT had no statistically significant effect on perinatal outcomes. However, when provided as treatment of antenatal anxiety during pregnancy, CBT seems to have a significant negative effect on both birth weight and gestational age.

Implications of all the available evidence

Initial evidence showing an adverse effect of an intervention might not translate into long-term adverse effects, since a recent study demonstrated no effects on child development at age 7.[87] While antenatal CBT seems to be effective in the prevention of postpartum depression, more evidence is needed on the effects on the offspring of specific groups of women that receive CBT during pregnancy. Extended and detailed follow-up is warranted for all groups to which CBT is provided.

Introduction

As many as 10-20% of all pregnant women suffer from symptoms of anxiety and depression during pregnancy,[1,2,213,214] which may adversely affect both maternal health and perinatal outcomes. A recent meta-analysis assessed thirty observational studies, which showed adverse effects of antenatal depression on perinatal outcomes.[12] Women, suffering from antenatal anxiety and depression symptoms tend to take less good care of themselves (e.g. neglecting personal hygiene, the occurrence of sleeping problems, disturbed drinking and smoking habits, denying prenatal care), which may influence the development of the foetus.[80,81] Other literature suggests that the prenatal effects of anxiety and depression on the child may be explained by the maternal stress system, i.e. overexposure to high glucocorticoid levels in the foetus which subsequently may hamper its growth and development.[21,217-219] Treatment of anxiety and depression during pregnancy may therefore help to improve perinatal outcomes.

Among adults, moderate to severe depression is usually treated using antidepressants.[220] Nevertheless, during pregnancy women prefer psychotherapy,[83] chiefly because the safety of medication as treatment of antenatal anxiety and depression cannot be warranted.[79,190,221] In the general population, cognitive behavioural therapy (CBT) has been shown to be effective as treatment of both anxiety and depression.[85,86] Therefore, current international guidelines recommend CBT as treatment during pregnancy.[74-77] However, evidence for the effectiveness of antenatal CBT on maternal symptoms and perinatal outcomes is sparse. Literature reports no randomised controlled trials (RCTs) assessing the effects of CBT on antenatal anxiety and only four RCTs that investigated the effects of CBT on depressive symptoms during pregnancy.[80-82,87] Although the latter RCT demonstrated no effects on offspring development at the age of seven years, none assessed perinatal outcomes.[87]

The aim of the present RCT was to investigate the effect of individual CBT for treatment of maternal anxiety and depression during pregnancy on perinatal outcomes, as compared to care as usual (CAU), and its mediation by antenatal symptoms of anxiety and depression. In the CBT arm, we expected higher birth weights, higher gestational age at birth, and higher Apgar scores, when compared to CAU.

Methods

Study design and participants

The present analyses used data from the 'Pregnancy Outcomes after a Maternity Intervention for Stressful EmotionS' (PROMISES) study. This multi-centre single-blind-CONSORT compliant RCT investigates the effects of CBT compared to CAU in pregnant women with symptoms of anxiety and depression on maternal symptom levels during and after pregnancy, perinatal outcomes and the child's development including behavioural and emotional problems. A detailed description of the PROMISES trial and results of the intervention on maternal mental symptoms were reported earlier.[224,237] Here we present the effects of the intervention on perinatal outcomes.

In the Netherlands, nearly 85% of all pregnant women with a low-risk pregnancy typically enter primary care and are monitored by independent midwives.[223] The remaining 15% are referred to a gynaecologist/obstetrician in a hospital.[223] All women visiting one of the participating midwifery practices (n=109) and obstetrics and gynaecology departments of hospitals (n=9) throughout the Netherlands were invited to participate in the population-based prospective Pregnancy Anxiety and Depression (PAD) study.[94] In brief, the PAD study investigated psychological, social, and medical factors during and after pregnancy. Women who provided written informed consent were screened for anxiety and depressive symptoms in their first trimester of pregnancy (T0), at a gestational age of 12 weeks. Gestational age was estimated using a transvaginal ultrasound dating scan, around 10 weeks of gestational age (GA). Women with at least moderate levels of anxiety and/or depressive symptoms and who indicated to be interested in a follow-up study, were invited to participate in the PROMISES trial. Levels of anxiety and depression were assessed using the Dutch versions of 6-item State Trait Anxiety Inventory (STAI) and 10-item Edinburgh Postnatal Depression Scale (EPDS), both validated for use during pregnancy.[95,112] For inclusion in the trial, the following cut-off values were used: STAI>42 and EPDS≥12.

Women fulfilling one or more of the following criteria were excluded from participation in the PROMISES trial: (1) High suicidal risk according to the suicidality subscale score on the MINI International Neuropsychiatric Interview [197]; (2) Presently receiving psychotherapy; (3) Substantial physical disease or illegal substance abuse; (4) No mastery of the Dutch language; or (5) Having a psychiatric history of bipolar disorder, psychoses or manic disorder.
Participating women were asked to fill out online questionnaires both during and after pregnancy. This study used data collected on the following occasions: screening at 12 weeks GA (T0), baseline information at 19 weeks GA (T1), follow-up questionnaires at 24 and 36 weeks GA (T2 and T3,

respectively) and 6 weeks postpartum (T4). Additionally, we derived perinatal data from standardised birth reports.

All women gave written informed consent. The medical ethical committee of the University Medical Center Groningen gave ethics approval for the study. The PROMISES trial was registered at Trialregister.nl, NTR2242.

Procedures

For the present analyses we used data on levels of anxiety and depression assessed four times during pregnancy (T0-T3) using STAI and EPDS questionnaires.[95,112] At baseline (T1) we assessed age, parity, socio-economic status (SES), and smoking status. The latter was reassessed at T3. Questions about SES were based on the Utrecht Health Project and used three indicators: family income and educational levels of both the pregnant woman and her partner. These indicators were equally weighted and categorised in tertiles, denoted as low SES, middle SES, and high SES.[99] To assess the presence of an anxiety, depressive, or comorbid (anxiety and depression) disorder according to the DSM-VI, the anxiety and mood disorder section of the Structured Clinical Interview for DSM-VI Disorders (SCID-I) was used at baseline.[204] At 6 weeks postpartum (T4), we assessed use of antidepressants and anxiolytics during pregnancy.

Power calculation

The present analyses included data of all 282 randomised participants. Given this sample size, an equal allocation rate, and based on an independent samples t-test (5% significance level, two-sided), we were able to detect at least an effect size of 0.33 or over with 80% power. We considered this effect size, which is approximately the midpoint of small (0.2) and moderate (0.5), relevant, given that previous studies among the general (patient) population indicated an effect size of around 0.4 or higher for anxiety and depression treatment.[85,86]

Randomisation

Eligible women were randomised immediately after baseline assessments, 1:1 to either CBT or CAU by an independent research assistant. A computer-generated randomisation sequence was used, stratified for parity and socio-economic position, with randomly permuted blocks of random size.

CBT Intervention

CBT trained, licensed psychologists throughout the Netherlands (n=31) delivered the intervention. All psychologists received an additional specific two-day training by a board certified clinical psychologist (CLHB). During this training all components of the intervention were explained and there was time for practice. CLHB developed the treatment protocol that consisted of 10-14 weekly individual sessions, of which 6-10 were scheduled to be delivered during pregnancy. The treatment encompassed optional modules with specific evidence-based CBT interventions focusing on the treatment of anxiety disorders, depressive disorders, or trauma, and post-traumatic stress disorder. The overall focus of the treatment was targeted at identifying and changing dysfunctional cognitions, and beliefs. Each session addressed pregnancy-related cognitions and attitudes. Moreover, all sessions were structured using homework assignments, and discussion of these assignments, and the rationale of each session was explained. A treatment manual is available on request. During the trial period, regular supervision was given by CLHB. Additionally, by organizing supervision sessions and using anonymous audiotapes of sessions, we warranted treatment integrity.

Control group

The control group received CAU, which consisted of the advice to contact their general practitioner and/or midwife because of an increased risk of developing an anxiety or depressive disorder. In view of the pragmatic nature of the trial, no restrictions were imposed on treatments in the CAU group. A full record of care provided was kept.

Outcomes

The perinatal outcomes of the present study were derived from standardised birth reports. They comprised birth weight, gestational age at delivery, and Apgar scores at 1, 5, and 10 minutes postpartum. The latter was estimated using a transvaginal ultrasound dating scan, around 10 weeks of gestational age. Besides, we assessed additional obstetric outcomes, including induced labour and caesarean section as dichotomous variables.

Statistical analyses

Characteristics of the study participants were described according to randomised group using appropriate descriptive analyses. Balance between the CBT and CAU groups was checked for age, symptoms of anxiety and depression, present DSM-IV diagnosis, and smoking status. Analyses were

additionally adjusted for these variables when they were unequally distributed across the groups, and in each per protocol analysis.

The perinatal outcomes gestational age, birth weight, and Apgar scores were analysed as continuous dependent variables using linear regression with the randomised group variable as the independent variable as well as the stratification variables parity and SES as recommended by Kernan et al.[238] To analyse whether results on birth weight are independent of gestational age, we performed additional analyses in which we adjusted the analyses of birth weight for the gestational age by adding the latter as independent variable. Primarily, the analyses were carried out according to the intention-to-treat principle. Secondary analyses were 'per protocol', i.e. restricted to those participants in the CBT group who had a minimum of six sessions and to those participants in the CAU group who did not visit a psychiatrist or psychologist.

Subgroup analyses were undertaken according to SES, parity, and the presence of an anxiety and/or depressive disorder according to DSM-IV. Additionally, we performed subgroup analyses on anxiety diagnosis, excluding posttraumatic stress disorder (PTSD), because of recent changes in DSM classification (DSM-V). Differences in effect of CBT between subgroups were evaluated by testing the statistical significance of treatment * subgroup interaction terms. All effect parameters were supplied with a 95% confidence interval (95% CI).

Post-hoc, mediation of above-mentioned associations by symptoms of anxiety and depression at T0, T1, T2, and T3 or by induced labour or caesarean section was assessed using the mediation model proposed by Preacher & Hayes.[239,240] In this model, linear and logistic regression analyses were used to investigate the statistically significant associations between CBT versus CAU and perinatal outcomes and which proportion of this association was mediated. We used 10,000 bootstrap estimates with replacement to obtain a 95% CI for each effect parameter, including the proportion mediated.

The percentage missing data ranged from 0 to 28.7 (depressive symptoms at 36 weeks GA) for the variables of main interest. We used multiple imputation by chained equations under the assumption that the missingness mechanism is missing at random (MAR) or missing completely at random (MCAR).[100] We imputed 20 datasets and data was pooled using Rubin's rules.[101] The imputation model included all variables that may predict missingness of a certain variable or its value. The missing data mechanism was studied for each of the variables, by predicting missingness of each of these variables from the other variables in the imputation model using multivariable logistic regression analyses. These analyses showed explained variances ranging from 12.3% to 36.5% (Nagelkerke's R^2), implying that data was at least partly missing at random, and consequently, multiple

imputation may have minimised bias. Multiple imputation is considered more reliable than solely complete case analyses.[224] Because the MAR nor the MCAR assumption can be proved we added complete case analyses as a sensitivity analysis. The level of statistical significance was set at 0.05, two-sided. Multiple imputation and all analyses were performed using SPSS Statistics 22 (IBM, USA).

Results

Between May 1, 2011, and Sept 1, 2014, following the screening of 8,143 pregnant women, a total of 1,284 women (16%) experienced at least moderate symptoms of anxiety and/or depression, of which 241 women were excluded, mostly because they were already receiving psychotherapy. The remaining 1,007 women were invited to participate in the PROMISES trial of which 282 women (28%) agreed to participate, of which 140 women received the CBT intervention and 142 received CAU (figure 1). Of these women, 241 (85%) birth reports were derived. At inclusion, the remaining 41 women gave no permission to retrieve their birth report. In the CBT group, 15 participants refused to start the intervention for various reasons, including no time or expecting that the treatment would be too burdensome. Participants who finished the intervention had a mean of nine sessions (range 1-15) and 93 participants completed six sessions during pregnancy. Thirty-two participants did not complete six sessions for various reasons (e.g. not presenting with symptoms anymore, no time, pregnancy complications). Only four participants used antidepressants, namely a selective sertraline reuptake inhibitor (SSRI), two in the CBT group and two in the CAU group. In both groups, one participant used the SSRI already at baseline and one started after randomisation. Four other participants used low dosed benzodiazepines, of which two in the CBT group and two in the CAU group. The two participants in the CBT group already used benzodiazepines and the two in the CAU group started after randomisation. As reported earlier, we found no evidence of a beneficial effect of CBT on maternal anxiety or depressive symptoms at 36 weeks of gestation, when compared to CAU.[237]

Characteristics of the participants are shown in table 1, according to randomisation status. Both groups were comparable on all variables, although participants in the CBT group more often presented with an anxiety or depression diagnosis and participants in the CAU group more often with a comorbid diagnosis. Each subsequent analysis was therefore supplemented with an additional analysis in which we added baseline diagnosis as independent variable. In the CBT group, 66 of the 121 children were girls (54.5%), in the CAU group 59 (49.2%).

Tables 2 and 3 show the differences between the CBT and CAU groups in mean birth weight and mean gestational age at birth. In our intention-to-treat analyses, offspring of participants in the CBT group showed overall a slightly lower birth weight and lower gestational age compared to the CAU group but differences were not statistically significant. Mean Apgar scores were exactly equal (1 minute: 8.6; 5 minutes: 9.5; 10 minutes 9.8) in both groups). After adjustment for imbalance between groups results remained similar.

Compared to the overall effectiveness estimates, the analyses in subgroups of SES and parity showed no statistically significant differences in effect size. The subgroup of women with low SES showed a negative effect on birth weight (β=-213.0 gram [95% CI -463.7 to 37.6]), but the corresponding interaction term was not statistically significant. However, in the subgroup of participants with a present DSM-IV anxiety diagnosis (N=98), we found that the mean birth weight was over 275 gram lower in the CBT group than in the CAU group (mean CBT=3354, CAU=3670 gram; β=-275.4 [95% CI -530.6 to -20.2]; interaction p=0.037). Besides, the gestational age was approximately a week lower in the CBT group, as compared to the CAU group (mean CBT=38.72, CAU=39.88 weeks; β=-0.978 [-1.872 to -0.084]; p=0.056). After adding gestational age to the analyses on birth weight, the results on birth weight were no longer significant. Excluding participants with PTSD diagnosis (N=14) did not substantially affect the results. Other subgroup analyses on present DSM-IV diagnosis did not show substantial differences in effect size.

Ninety-four participants in the CBT group (67.1%) received six or more sessions and thus were included in the per protocol analyses, as compared to the 132 participants in the CAU group (93.0%) who had not visited a psychiatrist or psychologist during pregnancy. Groups were balanced for the variables parity, smoking status, and SES, but not for age (p=0.27) and present diagnosis (p=0.01), therefore analyses were adjusted for the latter two variables. As shown in table 2 and 3, like in the intention-to-treat analyses, offspring of participants who completed six or more sessions showed overall a slightly lower birth weight and lower gestational age compared to the CAU group but differences were not statistically significant. In the subgroup analyses on participants who completed six or more sessions, we found a more pronounced negative effect of CBT on birth weight, i.e. that for the group of women with a DSM-IV anxiety diagnosis (N=81), the mean birth weight was over 300 gram lower in the CBT group (mean CBT=3335, CAU=3640 gram; β=-338.0 [95% CI -605.5 to -70.6]; interaction p=0.017) and the gestational age was more than a week lower in the CBT group, as compared to the CAU group (mean CBT=38.70, CAU=39.71 weeks; β=-1.079 [-1.904 to -0.254]; p=0.010). After adding gestational age to the analyses on birth weight, the results on birth weight were no longer significant. Excluding participants with PTSD diagnosis did not substantially affect the results. Other subgroup analyses on parity or present DSM-IV diagnosis did not show substantial differences in effect size.

Post-hoc exploratory mediation analyses showed that in the group of women with a DSM-IV anxiety diagnosis, the adverse effect of CBT on birth weight but not on gestational age was partly (22.6%) but not statistically significantly mediated by symptom level of anxiety at T2 (mean STAI scores: CBT group 47.80 vs. CAU group 47.64; total effect β=-386.3 gram [95% CI -693.2 to -79.4]; p=0.014, indirect effect β=-87.4 [-211.5 to 7.3]; p=0.148). The analyses showed no mediating effects of symptom levels of anxiety at T1

or T3, symptom levels of depression at T1, T2 or T3, induced labour (CBT group N=36 [29.8%] vs. CAU group N=32 [26.7%]) or caesarean section (22 [18.2%] vs. 21 [17.5%]). Per protocol mediation analyses showed similar results.

Subgroup and post-hoc analyses using Apgar scores as outcome variables did not show any difference between both groups. Adjustment of all analyses for age and smoking status did not substantially affect the results. Neither did exclusion of participants who used antidepressants or benzodiazepines during pregnancy. Missingness of assessed variables was similar in both groups. Results from complete case analyses did not substantially differ from multiple imputation analyses.

Figure 1: Trial profile

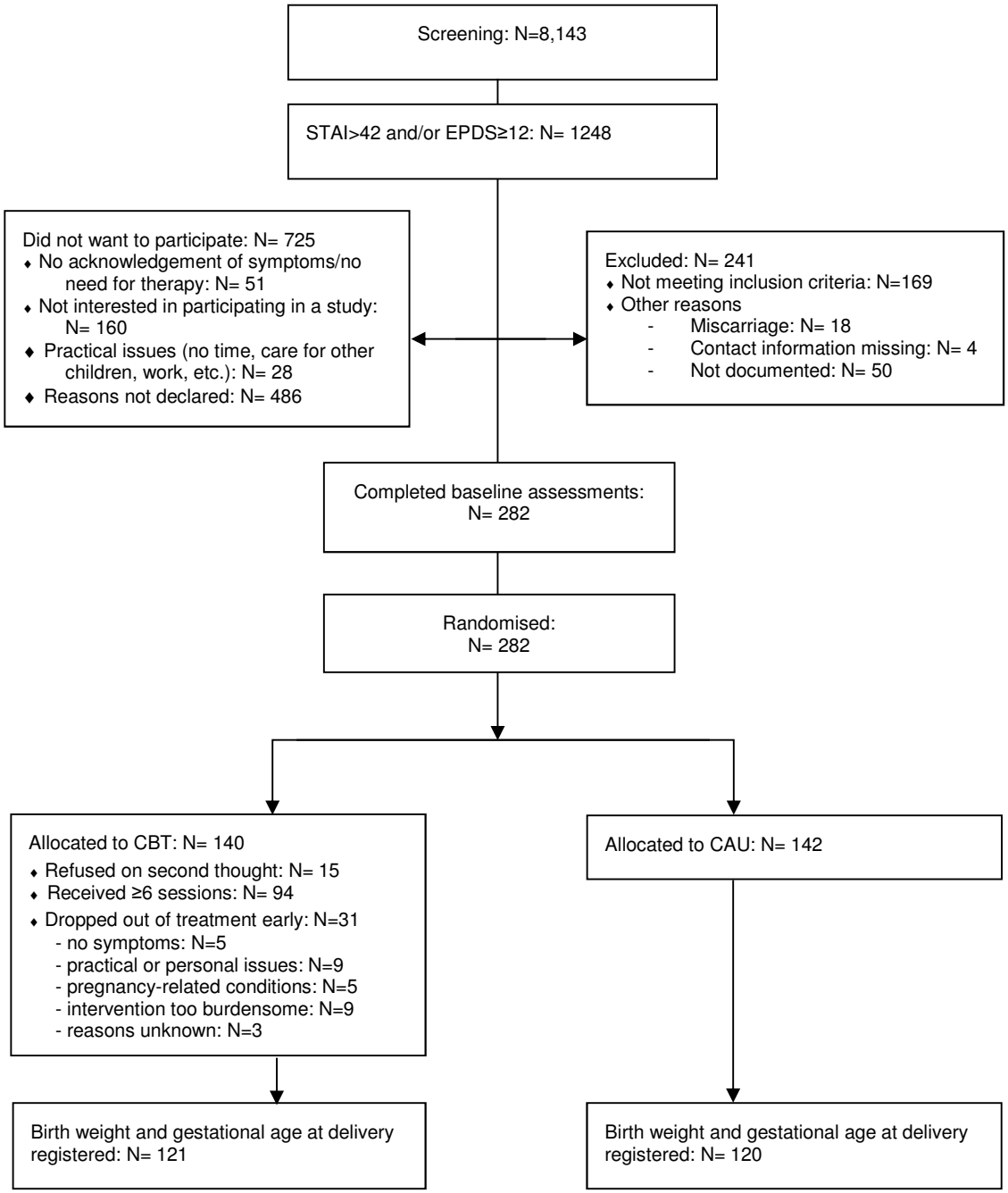

Table 1: Characteristics of participants

	Intervention (N=140)	**Care as usual (N=142)**
	Mean (SD)	***Mean (SD)***
Age in years	34.8 (4.6)	33.7 (4.5)
STAI-score screening (T0)	49.7 (7.8)	49.3 (7.5)
EPDS-score screening (T0)	10.1 (4.2)	10.1 (4.1)
	N (%)	***N (%)***
Multiparous	70 (50.0)	73 (51.4)
Current smoking status	17 (12.1)	16 (11.3)
Socio-economic status		
Low	48 (34.3)	51 (35.9)
Moderate	36 (25.7)	35 (24.6)
High	56 (40.0)	56 (39.4)
Present diagnosis (DSM-IV)		
Anxiety	57 (40.7)	41 (28.9)
Depression	14 (10.0)	9 (6.3)
Anxiety and depression	14 (10.0)	20 (14.1)

STAI= State Trait Anxiety Inventory.
EPDS= Edinburgh Postnatal Depression Score.
DSM-IV= Diagnostic and Statistical Manual of Mental Disorders 4th edition.

Table 2: Effect of CBT on birth weight, as compared to CAU.

	Intervention (N=140)	**Care as usual (N=142)**
Birth weight, grams (SD)	3419 (651)	3474 (561)
	Intention-to-treat analyses	
	Mean difference (95% CI)	**p value**
MICE (N=282)	-54.5 (-200.0; 90.7)	0.462
Complete case analysis (N=241)	-48.9 (-197.5; 99.7)	0.517
Subgroups (MICE)		
Present diagnosis		
No diagnosis (N=127)	28.2 (-184.3; 240.7)	0.794
*CBT/CAU * No diagnosis*		0.312
Anxiety diagnosis (N=98)	-275.4 (-530.6; -20.2)	**0.034**
*CBT/CAU * Anxiety diagnosis*		**0.037**
Depression diagnosis (N=23)	-15.1 (-581.9; 551.8)	0.958
*CBT/CAU * Depression diagnosis*		0.906
Comorbid diagnosis (N=34)	192.4 (-268.6; 653.3)	0.413
*CBT/CAU * Comorbid diagnosis*		0.286
	Per protocol analyses	
	Adjusted mean difference (95% CI)	**p value**
MICE (N=226)	-73.4 (-228.9; 82.2)	0.355
Complete case analysis (N=188)	-62.6 (-219.4; 94.2)	0.432
Subgroup analyses (MICE)		
Present diagnosis		
No diagnosis (N=99)	110.5 (-139.4; 360.4)	0.386
*CBT/CAU * No diagnosis*		0.088
Anxiety diagnosis (N=81)	-338.0 (-605.5; -70.6)	**0.013**
*CBT/CAU * Anxiety diagnosis*		**0.017**
Depression diagnosis (N=20)	-108.1 (-758.1; 541.9)	0.745
*CBT/CAU * Depression diagnosis*		0.819
Comorbid diagnosis (N=26)	96.7 (-351.4; 544.7)	0.421
*CBT/CAU * Comorbid diagnosis*		0.667

*Differences between groups are analysed using linear regression and are adjusted for parity, socio-economic status, age, and present diagnosis where appropriate. Subgroups were classified according to DSM-IV diagnosis anxiety, depression and comorbid diagnosis (anxiety and depression). Differences in effect of CBT between subgroups were evaluated by testing the statistical significance of treatment * subgroup interaction terms. Complete case analyses showed similar results. Bold numbers are p<0.05.*

MICE= multiple imputation by chained equations.

DSM-IV= Diagnostic and Statistical Manual of Mental Disorders 4th edition.

Table 3: Effect of CBT on gestational age at birth, as compared to CAU.

	Intervention (N=140)	**Care as usual (N=142)**
Gestational age, weeks (SD)	38.94 (2.33)	39.20 (1.81)
	Intention-to-treat analyses	
	Mean difference (95% CI)	**p value**
MICE (N=282)	-0.257 (-0.758; 0.243)	0.313
Complete case analysis (N=241)	-0.277 (-0.803; 0.249)	0.301
Subgroups (MICE)		
Present diagnosis		
No diagnosis (N=127)	-0.025 (-0.794; 0.745)	0.950
*CBT/CAU * No diagnosis*		0.389
Anxiety diagnosis (N=98)	-0.978 (-1.872; -0.084)	**0.032**
*CBT/CAU * Anxiety diagnosis*		0.056
Depression diagnosis (N=23)	-0.028 (-1.677; 1.620)	0.973
*CBT/CAU * Depression diagnosis*		0.728
Comorbid diagnosis (N=34)	0.719 (-0.578; 2.017)	0.277
*CBT/CAU * Comorbid diagnosis*		0.233
	Per protocol analyses	
	Adjusted mean difference (95% CI)	**p value**
MICE (N=226)	-0.247 (-0.764; 0.270)	0.348
Complete case analysis (N=188)	-0.197 (-0.748; 0.354)	0.481
Subgroup analyses (MICE)		
Present diagnosis		
No diagnosis (N=99)	0.240 (-0.671; 1.152)	0.605
*CBT/CAU * No diagnosis*		0.255
Anxiety diagnosis (N=81)	-1.079 (-1.904; -0.254)	**0.010**
*CBT/CAU * Anxiety diagnosis*		**0.017**
Depression diagnosis (N=20)	-0.202 (-2.133; 1.729)	0.838
*CBT/CAU * Depression diagnosis*		0.579
Comorbid diagnosis (N=26)	1.072 (-0.519; 2.662)	0.186
*CBT/CAU * Comorbid diagnosis*		0.240

*Differences between groups are using linear regression and are adjusted for parity, socio-economic status, age, and present diagnosis where appropriate. Subgroups were classified according to DSM-IV diagnosis anxiety, depression and comorbid diagnosis (anxiety and depression). Differences in effect of CBT between subgroups were evaluated by testing the statistical significance of treatment * subgroup interaction terms. Complete case analyses showed similar results. Bold numbers are p<0.05.*

MICE= multiple imputation by chained equations.

DSM-IV= Diagnostic and Statistical Manual of Mental Disorders 4th edition.

Discussion

The present study investigated the effects of antenatal CBT in women with at least moderate levels of anxiety and/or depressive symptoms on perinatal outcomes, compared to CAU. Overall in our intention-to-treat analyses, we did not find a statistically significant effect of CBT on major perinatal outcomes, but we did find a significant adverse effect on birth weight and gestational age at delivery in women with an anxiety diagnosis. Our per-protocol analyses demonstrated an even stronger association. After adding gestational age to the analyses on birth weight, the results on birth weight were no longer significant, indicating that the adverse effects mainly apply to gestational age and that the offspring is not small for gestational age. The adverse effects could not be explained by use of antidepressants or benzodiazepines, higher proportions of induced labour or caesarean section, smoking, or symptom levels of depression, but may partly be explained by the anxiety symptom level during pregnancy, which was increased in the CBT group relative to the women who received CAU.

In current international guidelines, together with antidepressants of which adverse perinatal effects are increasingly studied, CBT is the preferred treatment option for anxiety and depression.[73-76] Nevertheless, evidence for the effectiveness of CBT during pregnancy on both maternal symptoms and perinatal outcomes is sparse. It is believed that CBT has a positive effect on maternal symptoms and furthermore may discourage the well-documented adverse effects of psychopathology on perinatal outcomes. Accordingly, we hypothesised that CBT would have a positive effect on birth weight, gestational age, and Apgar scores. However, we found neither a statistically significant overall effect of CBT on major perinatal outcomes, nor in the subgroup analyses. Furthermore, our study showed a strong and significant adverse effect of CBT in pregnant women with DSM-IV anxiety diagnosis on birth weight and gestational age, when compared to CAU. The demonstrated adverse effect sizes are considerable and are much larger than the widely acknowledged adverse effects of, for example, smoking and indoor air pollution during pregnancy.[24,41]

Limitations of this study include the low participation rate of women who were invited to participate in the trial. Only 282 (28%) of the eligible 1,007 women agreed to participate in our RCT. Our response rate was slightly low when compared to that of other similar studies that included pregnant women who were not active help-seekers. The study of Austin et al. included pregnant women with subclinical symptoms or anxiety and depressive disorders and showed a slightly higher response rate of 39%.[82] The study by Le et al. included women with subclinical symptoms or a previous depression had an even higher response rate of 70%.[81] A further limitation was that we were unable to measure cortisol levels, (nor)adrenal hormones or other biological parameters in the present study. Such physiological stress measurements could have provided us with more information about the

mediators of the effects of CBT during pregnancy that we observed. Additionally, in our per protocol analyses we excluded women in the CAU group who visited a psychiatrist or psychologist during pregnancy. Consequently, these women may form the most severe cases and excluding them may have altered our results. Finally, our study demonstrated a strong adverse effect in a subgroup analysis, which requires replication. On the other hand, strengths of this study should be mentioned. To our knowledge, this study is the first RCT investigating the effect of CBT during pregnancy on perinatal outcomes. We included a population-based sample that may allow us to generalise our findings to a larger Dutch pregnant population presenting with anxiety and/or depressive symptoms, as opposed to if we had recruited a sample from clinical settings only. Our response rate was fairly high and we used multiple imputation in dealing with missing values. This is considered more reliable than solely complete case analyses.[224] Furthermore, we used the widely validated Structured Clinical Interview for DSM-VI Disorders (SCID-I) to assess the presence of an anxiety or depressive disorder according to the DSM-VI and a manualised CBT intervention utilised by trained CBT psychologists to increase reliability.

The main focus of our CBT treatment was targeted on teaching the patient to identify and challenge dysfunctional cognitions and beliefs. Additionally, optional modules were available, focusing on specific treatment of depression (behavioural activation), anxiety (exposure), or post-traumatic stress disorder (exposure: imagery and rescripting).

Although scarcely studied, very limited literature suggests that CBT may have adverse (side) effects.[242] Providing CBT for anxiety symptoms on one hand treats symptoms, but on the other hand confirms that there are symptoms and the (expected) exposure increases anxiety of the short term, that these are disadvantageous, and that these should be treated.[243] The latter thoughts may increase anxiety symptoms, instead of decreasing them. Our mediation analysis shows that the difference in birth weight between both groups is partly mediated by anxiety symptom levels at T2, i.e. at 24 weeks of pregnancy. In our CBT treatment, this is the moment when women receive their first sessions. Consequently, we propose that the demonstrated adverse effects may be due to increased stress levels, conceivably induced by the provided CBT. Indeed, the dialogs and exposure during the sessions in CBT may be confrontational and may induce stress in the short-term, instead of reducing stress levels. Our per-protocol analyses, wherein perinatal outcomes of women who received at least six CBT sessions were compared with women who received CAU, demonstrated even stronger adverse effects, suggesting an exposure-response mechanism: the more CBT sessions the women received, the worse the perinatal outcomes.

While we observed unexpected results, this study has major clinical significance. In contrast to what is commonly believed, CBT may not positively affect perinatal outcomes, but in fact CBT may have an adverse

effect, when provided as early treatment in pregnant women with a DSM-IV anxiety diagnosis. Additionally, in pregnant women with a DSM-IV depression diagnosis, or without any DSM-IV diagnosis, neither positive nor adverse effects of CBT on perinatal outcomes were observed. Therefore, although antenatal CBT is most likely to be effective for prevention of postpartum depression, CBT should not be provided as a prevention of low birth weight or prematurity and should be reconsidered as an antenatal treatment of anxiety symptoms given the possible long-term effects of both low birth weight and low gestational age.

Further research is needed on antenatal treatment options in women with anxiety disorders, wherein perinatal outcomes should be studied. Additionally, future studies could explore potential underlying biological mechanisms and the long-term effect of CBT during pregnancy on the offspring.

CHAPTER 10

Effects of cognitive behavioural therapy during pregnancy on behavioural problems and development in offspring: the PROMISES randomised controlled trial

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Abstract

Background

From observational prospective studies, there is ample evidence that maternal depression or anxiety during pregnancy is an important risk factor for adverse psychosocial outcomes in the offspring. However, no previous study has shown that treatment of depressive/anxious symptoms in pregnancy prevents psycho-social problems in the offspring and may eventually bring down the public health burden of mental disease. The aim of this study was to assess the effects of cognitive behavioural therapy in pregnant women with symptoms of anxiety or depression on behavioural and emotional problems and the child's development.

Methods

We performed a multi-centre, single-blind randomised controlled trial in pregnant women with depressive and/or anxiety symptoms who visited one of the participating 109 midwifery practices or nine hospitals. We enrolled women with at least moderate symptoms of depression (EPDS≥12) and/or anxiety (STAI>42). Participants were randomised (1:1) by computer-generated sequence to receive either antenatal CBT or care as usual (CAU), stratified by parity, and socio-economic status. The present analyses assessed behavioural and developmental problems as well as cognitive, fine and gross motor development on both intention-to-treat and per-protocol.

Findings

Of the 1007 women invited, 282 (28%) were randomised to receive antenatal CBT (n=140) or CAU (n=142) between April 1, 2011, and Sept 1, 2014. No substantial baseline differences were observed. The present analyses included 196 women (CBT N=97, CAU N=99). No substantial baseline differences were observed. Offspring of participants in the CBT group showed overall slightly higher child behaviour problems and lower developmental scores compared to the CAU group but differences were not statistically significant. Differences in CBCL scores: internalising problems: 0.672 [95%CI -0.331; 1.675], externalising problems: 0.190 [-1.550; 1.931], sleep problems: 0.015 [-0.521; 0.552], total problems 0.973 [-2.530; 4.476]. Differences in scaled BSID-III scores: cognitive: -0.315 [-0.887; 0.258], fine motor -0.235 [-1.050; 0.580], and gross motor -0.067 [-0.831; 0.698]. Results of subgroup analyses and per-protocol analyses were similar.

Conclusions

The present study found no evidence of a beneficial effect of antenatal CBT for the offspring, as compared to CAU. Further research is needed to assess whether other treatment options of antenatal psychopathology have more promising results.

Introduction

The global burden of diseases caused by mental disorders is huge and at least comparable to the burden caused by many severe physical diseases. It was estimated that 50% of all daily adjusted life years (DALY's) in the 15-44 years old are due to nine psychiatry-related conditions.[29] In addition, depressive disorders are projected to rank second on a list of fifteen major diseases in terms of burden of disease in 2030.[181] Furthermore, a substantial part of the costs is caused by new cases, which accounts for 39.2% of the costs at population level.[182] In summary, prevention of mental disorders is essential.

Maternal antenatal anxiety or depression is an important and possibly modifiable risk factor for cognitive, behavioural and emotional problems among the offspring children.[4,15-20] Of all women, 10-20% suffers from symptoms of depression or anxiety during pregnancy.[1,2,93,184,185] The effects of these symptoms on the child's psychosocial problems are considerable: up to 22% of the variance in behavioural problems is linked with antenatal anxiety, stress or depression.[19] These adverse effects on offspring seem to be lasting. For example, antenatal maternal anxiety was related to behavioural or emotional problems of 4 year old children, independent of maternal postnatal depression or anxiety,[4] and higher maternal anxiety symptom levels early during pregnancy were related to an increase in ADHD and other externalizing problems in their 8-9 year old children.[186]

There are several mechanisms through which antenatal anxiety and depression could have an adverse effect on the offspring, which can be divided into direct and indirect. A direct mechanism that has been subject of study for decades is one in which depression or anxiety activates the maternal stress system leading to e.g. elevated glucocorticoid levels, which subsequently adversely influence the development and long-term physiology of the foetus' brain by passing the placenta.[244] This so-called "early life programming" has been a popular hypothesis for the explanation of not only brain disorders but has been suggested to play a role in cardiovascular disease as well.[21,22] Furthermore, epigenetic variation(s) has been proposed as mediating mechanism in linking early life exposures to long-term psychological and behavioural outcomes.[23]

However, because all earlier research on this topic is observational, confounding by genetics or environment could not be excluded. Indeed, the effects of maternal stress during pregnancy on the developing foetus may also be (partly) indirect. Women, suffering from antenatal anxiety and depression symptoms have tend to take less good care of themselves (e.g. neglecting personal hygiene, the occurrence of sleeping problems, disturbed drinking and smoking habits, denying prenatal care), what may influence the development of the foetus.[24-27] Another indirect way in which depression might influence offspring mental development is when the antenatal depression remains after delivery and turns into a postnatal depression. In

this way, because the mother has a reduced ability to respond to the child, mother-child attachment might be endangered, which in turn is associated with offspring cognitive, behavioural and emotional problems.[29-32] Additionally, associations of antenatal anxiety and depression with adverse outcomes in the offspring might be explained by a shared genetic or environmental predisposition between mother and child.

Whatever the actual mechanism(s) involved is/are, there is presently convincing evidence that children whose mothers suffered from anxiety or depression during pregnancy have an increased risk of behavioural and emotional problems. On population level, substantial total mental health gains may be accomplished when depressed or anxious women are adequately treated during their pregnancy, even if the effect size of the treatment is only relatively small. However, this is only true if the association is causal, i.e. not explained by shared genetic or environmental make-up between mother and child.

Psychological therapies in the treatment of both depression and anxiety have been proven effective during the past 50 years, especially cognitive behavioural therapy (CBT).[86,88,187-189] Although current guidelines state that medication is an alternative effective treatment, pregnant women prefer psychological treatment,[185] mainly because the safety of medication to treat antenatal anxiety and depression cannot be guaranteed.[190]

While literature provides ample evidence for an effect of CBT in preventing postpartum depression, literature reports no randomised controlled trials (RCTs) assessing the effects of CBT on antenatal anxiety. Four RCTs investigated the effects of CBT on depressive symptoms during pregnancy from which only one assessed offspring development in Pakistan.[80-82,87] The latter study showed no effect of antenatal CBT on offspring cognitive, socio-emotional, or physical development at age 7. Nevertheless, this study only assessed parent-reported child development, what may have been subject to reporting bias, and no offspring behavioural problems.[87]

The aim of the present RCT was to assess the effects of individual CBT as compared to care as usual (CAU) on the offspring's behavioural and emotional problems and cognitive, fine and gross motoric development.

Methods

Study design and participants

The present study used data from the 'Pregnancy Outcomes after a Maternity Intervention for Stressful EmotionS' (PROMISES) trial. This multi-centre single-blind-CONSORT compliant [245] randomised controlled trial investigates the effects of CBT compared to CAU in pregnant women with symptoms of anxiety and depression on maternal symptom levels during and after pregnancy, perinatal outcomes and the child's development including behavioural and emotional problems. A detailed description of the PROMISES trial and results of the intervention on both maternal mental symptoms and perinatal outcomes were published earlier.[222,237,246] In this manuscript we report on the effects of the intervention on the offspring's behavioural and emotional problems and cognitive, fine and gross motoric development.

In the Netherlands, approximately 85% of all pregnant women with low-risk pregnancies typically enter primary care and are monitored by independent midwives.[223] The remaining 15% are referred to a gynaecologist/obstetrician in a hospital.[223] All women visiting one of the participating midwifery practices (n=109) and obstetrics and gynaecology departments of participating hospitals (n=9) throughout the Netherlands were invited to participate in the population-based Pregnancy Anxiety and Depression study (PAD).[94] In brief, this prospective cohort study investigated psychological, social, and medical factors during and after pregnancy. Women who provided written informed consent were screened for anxiety and depressive symptoms in their first trimester of pregnancy (T0), i.e. 12 weeks gestational age (GA). Women with at least moderate levels of anxiety and/or depressive symptoms and who indicated to be interested in a follow-up study, were invited to participate in the PROMISES trial. Levels of anxiety and depression were assessed using the Dutch versions of 6-item State Trait Anxiety Inventory (STAI) and 10-item Edinburgh Postnatal Depression Scale (EPDS), both validated for use during pregnancy.[95,112] For inclusion in the trial, the following cut-off values were used: STAI>42 and EPDS≥12.

Women fulfilling one or more of the following criteria were excluded from participation in the PROMISES trial: (1) High suicidal risk according to the suicidality subscale score on the MINI International Neuropsychiatric Interview [197]; (2) Presently receiving psychotherapy; (3) Substantial physical disease or illegal substance abuse; (4) No mastery of the Dutch language; or (5) Having a psychiatric history of bipolar disorder, psychoses or manic disorder.
Participating women were asked to fill out online questionnaires both during and after pregnancy. The present analyses used data collected on the following occasions: screening at 12 weeks GA (T0), baseline information at 19 weeks GA (T1), and follow-up measurements at around 18 months postpartum (T2).

All women gave written informed consent. The medical ethical committee of the University Medical Center Groningen gave ethics approval for the study. The PROMISES trial was registered at Trialregister.nl, NTR2242.

Procedures

For the present analyses we used data on levels of anxiety and depression at screening (T0) using STAI and EPDS questionnaires.[95,112] At baseline (T1) we assessed age, parity, socio-economic status (SES), and smoking status. Questions about SES were based on the Utrecht Health Project and used three indicators: family income and educational levels of both the pregnant woman and her partner. These indicators were equally weighted and categorised in tertiles, denoted as low SES, middle SES, and high SES.[99] To assess the presence of an anxiety, depressive, or comorbid (anxiety and depression) disorder according to the DSM-VI, the anxiety and mood disorder section of the Structured Clinical Interview for DSM-VI Disorders (SCID-II) was used at baseline.[204]

Power calculation

The present analysis included data of 196 randomised participants (CBT N=97, CAU N=99). Given this sample size, an equal allocation rate, and based on an independent samples t-test (5% significance level, two-sided), we were able to detect at least an effect size of 0.4 or over with 80% power. We considered this effect size relevant, given that previous studies among the general (patient) population indicated an effect size of around 0.4 or higher for anxiety and depression treatment.[85,86]

Randomisation

Eligible women were randomised immediately after baseline assessments, 1:1 to either CBT or CAU by an independent research assistant. To this end, a computer-generated randomisation sequence was used, stratified for parity and socio-economic position, with randomly permuted blocks of random size.

CBT Intervention

CBT trained, BIG registered psychologists throughout the Netherlands (n=31) delivered the intervention. All psychologists received an additional specific two-day training by a board certified clinical psychologist (CLHB). During this training all components of the intervention were explained and there was time for practice. CLHB developed the treatment protocol that consisted of 10-14 weekly individual sessions, of which 6-10 were scheduled to be delivered during pregnancy. The treatment encompassed optional modules with specific evidence-based CBT interventions focusing on the treatment of anxiety disorders, depressive disorders, or trauma, and post-traumatic stress disorder. The overall focus of the treatment was targeted at

identifying and changing dysfunctional cognitions, and beliefs. Each session addressed pregnancy-related cognitions and attitudes. Moreover, all sessions were structured using homework assignments, and discussion of these assignments, and the rationale of each session was explained. A treatment manual is available on request. During the trial period, regular supervision was given by CLHB. Additionally, by organizing supervision sessions and using anonymous audiotapes of sessions, we warranted treatment integrity.

Control group

The control group received CAU, which was advice to contact their general practitioner and/or midwife because of an increased risk of developing an anxiety or depressive disorder. In view of the pragmatic nature of the trial, no restrictions were imposed on treatments in the CAU group. A full record of care provided was kept.

Outcomes

At age 18 months, the behavioural and developmental problems, as well as the cognitive, fine and gross motor development in offspring of participants were assessed.

Behavioural and developmental problems were assessed using the Child Behaviour Check List for children of age 1.5 to 5 (CBCL 1.5–5) including the Caregiver-Teacher Report form (C-TRF).[208] This well established, reliable and valid scale designed for parents and caregivers comprises seven syndrome scales: emotionally reactive, anxious depressed, somatic complaints, withdrawn, sleep problems, attention problems and aggressive problems. In addition, it contains scales for internalising, externalising and total problems. Symptom scores may further be related to formal DSM-diagnostic criteria. The CBCL 1.5-5 is considered a sensitive instrument also deployed in several earlier studies.[211,212] For the assessment of psychopathology in preschool children it is considered essential to obtain information from different sources.[209] Therefore we decided to include the C-TRF for the caregivers of the children other than their parents. Parents were instructed to hand these lists to the actual other caregivers of their children, e.g. grandparents, baby-sitters, kindergarten-coaches, et cetera.

Cognitive, fine and gross motor development levels were assessed using the Bayley III Scales of Infant and Toddler Development (BSID-III).[205] It was individually administered and consisted of three subscales: cognitive development (mental development index), gross and fine motor development. This tool is widely used in both research and clinical settings and is considered the best and most applied method for the assessment of the child's development to date.[206] Importantly, the instrument has shown to be sensitive. In the context of our study, maternal anxiety in pregnancy explained as much as 11% of the variance in the Bayley scores in a study among two-year-old toddlers.[207] All participating women received invitations

for the BSID-III when their offspring aged 18 months. Tests were performed in hospitals or at participant's homes. Trained research assistants masked to study group provided the cognitive and motor scales. Inter-observer variance was limited by providing supervision after reviewing and reassessing videotaped BSID-III assessments. The BSID-III outcomes were reported as composite scales with an age-dependent normed mean of 100 and a SD of 15.[205]

Statistical analyses

Characteristics of the study participants were described according to randomised group using appropriate descriptive analyses. Balance between the CBT and CAU groups was checked for age, symptoms of anxiety and depression, present DSM-IV diagnosis, and smoking status. Analyses were additionally adjusted for these variables when they were unequally distributed across the groups, and in each per protocol analysis.

CBCL scores administered by parents and other caregivers were averaged. CBCL and BSID-III scores were analysed as continuous dependent variables using linear regression with the randomised group variable as independent variable as well as the stratification variables parity and SES as recommended by Kernan et al.[238] Primarily, the analyses were carried out according to the intention-to-treat principle. Secondary analyses were 'per protocol', i.e. restricted to those participants who had a minimum of 6 sessions.

Subgroup analyses were undertaken according to SES, parity, and the presence of an anxiety and/or depressive disorder according to DSM-IV. Differences in effect of CBT between subgroups were evaluated by testing the statistical significance of treatment * subgroup interaction terms. All effect parameters were supplied with a 95% confidence interval (95% CI).

The percentage missing data ranged from 0 to 39.4 (BSID-III scores) for the variables of main interest. We used multiple imputation by chained equations under the assumption that the missingness mechanism is missing at random (MAR) or missing completely at random (MCAR).[100] We imputed 20 datasets and data was pooled using Rubin's rules.[101] The imputation model included all variables that may predict missingness of a certain variable or its value. The missing data mechanism was studied for each of the variables, by predicting missingness of each of these variables from the other variables in the imputation model using multivariable logistic regression analyses. These analyses showed explained variances ranging from 4.2% to 12.3% (Nagelkerke's R^2), implying that data was at least partly missing at random, and consequently, multiple imputation may have minimised bias. Multiple imputation is considered more reliable than solely complete case analyses.[224] Because the MAR nor the MCAR assumption can be proved we added complete case analyses as a sensitivity analysis. The level of statistical significance was set at 0.05, two-sided. Multiple imputation and all analyses were performed using SPSS Statistics 22 (IBM, USA).

Results

Between May 1, 2011, and Sept 1, 2014, following the screening of 8143 pregnant women, a total of 1284 women (16%) experienced at least moderate symptoms of anxiety and/or depression, of which 241 women were excluded, mostly because they were already receiving psychotherapy. The remaining 1007 women were invited to participate in the PROMISES trial of which 282 women (28%) agreed to participate, of which 140 women received the CBT intervention and 142 received CAU (figure 1). Among the offspring of these 282 participants, in 175 children (62%; CBT N=90, CAU N=85) CBCL scores were assessed at mean 18.5 months of age (SD=1.5), and in 171 children (61%; CBT N=83, CAU N=88) BSID-III scores were assessed at mean 22.0 months of age (SD=2.7).

In the CBT group, 15 participants refused to start the intervention for various reasons, including no time or expecting that the treatment would be too burdensome. Participants who finished the intervention had a mean of nine sessions (range 1-15) and 93 participants completed six sessions during pregnancy. Thirty-two participants did not complete six sessions for various reasons (e.g. not presenting with symptoms anymore, no time, pregnancy complications). Only four participants used antidepressants, namely a selective sertraline reuptake inhibitor (SSRI), two in the CBT group and two in the CAU group. In both groups, one participant used the SSRI already at baseline and one started after randomisation. Four other participants used low dosed benzodiazepines, of which two in the CBT group and two in the CAU group. The two participants in the CBT group already used benzodiazepines and the two in the CAU group started after randomisation.

Characteristics of the participants are shown in table 1, according to randomisation status. Both groups were comparable on all variables, although participants in the CBT group more often presented with an anxiety or depression diagnosis and participants in the CAU group more often with a comorbid diagnosis. Each subsequent analysis was therefore supplemented with an additional analysis in which we added baseline diagnosis as independent variable.

Table 2 shows the differences between the CBT and CAU groups in CBCL and BSID-III scores. In our intention to treat analyses, offspring of participants in the CBT group had slightly more behavioural problems and lower developmental scores compared to the CAU group but differences were not statistically significant. After adjustment for imbalance between groups results remained similar.

Analyses on subgroups of SES, parity, and present DSM-IV diagnosis showed no significant differences in effect size either.

Ninety-four participants in the CBT group (67.1%) received six or more sessions and thus were included in the per protocol analyses, as compared to the 132 participants in the CAU group (93.0%) who had not visited a psychiatrist or psychologist during pregnancy. Groups were balanced for the variables parity, smoking status, and SES, but not for age (p=0.27) and present diagnosis (p=0.01), therefore analyses were adjusted for the latter two variables. As shown in table 2, like in the intention to treat analyses, offspring of participants in the CBT group had slightly more behavioural problems and lower developmental scores compared to the CAU group but differences were not statistically significant.

Adjustment of all analyses for age and smoking status did not substantially affect the results. Missingness of assessed variables was similar in both groups. Results from complete case analyses did not substantially differ from multiple imputation analyses.

Figure 1: Trial profile

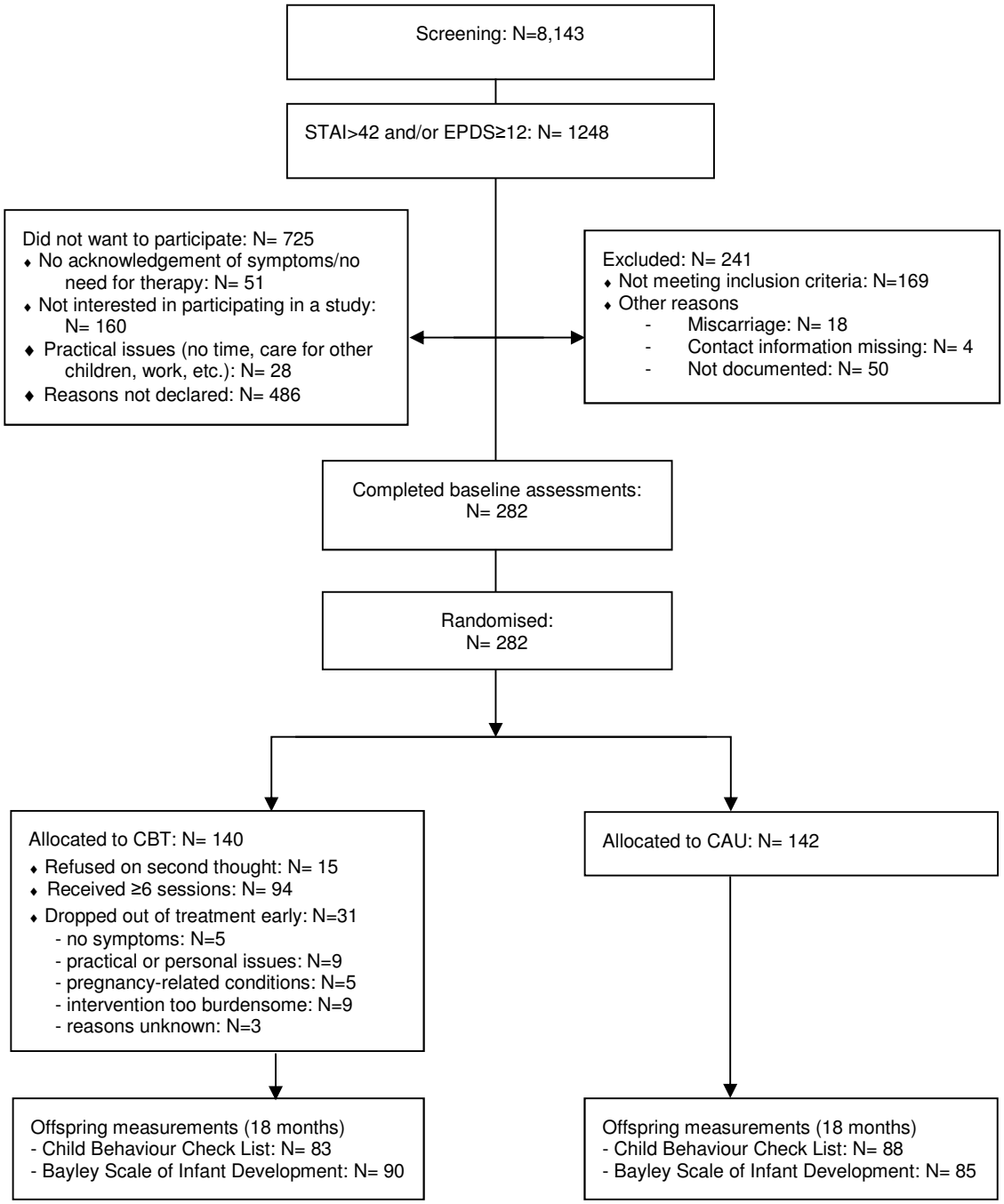

Table 1: Characteristics of participants

	Intervention (N=140)	**Care as usual (N=142)**
	Mean (SD)	***Mean (SD)***
Age in years	33.4 (4.6)	32.1 (4.5)
STAI-score screening (To)	48.6 (8.7)	48.5 (8.4)
EPDS-score screening (To)	9.8 (4.1)	9.7 (4.1)
	N (%)	***N (%)***
Multiparous	70 (50.0)	73 (51.4)
Smoking (baseline)	17 (12.1)	16 (11.3)
Socio-economic status		
Low	48 (34.3)	51 (35.9)
Moderate	36 (25.7)	35 (24.6)
High	56 (40.0)	56 (39.4)
Present diagnosis (DSM-IV)		
Anxiety	58 (41.4)	41 (28.9)
Depression	15 (10.7)	9 (6.3)
Anxiety and depression	20 (14.3)	15 (10.6)

STAI= State Trait Anxiety Inventory.
EPDS= Edinburgh Postnatal Depression Score.
DSM-IV= Diagnostic and Statistical Manual of Mental Disorders 4th edition.

Table 2: Developmental and behavioural problems, and cognitive and motor development. Values are means (SD) unless stated otherwise.

	Intervention (N=140)	**Care as usual (N=142)**
Child behaviour (CBCL)		
Internalising problems score	4.59 (3.48)	3.94 (3.16)
Externalising problems score	9.71 (5.48)	9.54 (6.46)
Sleep problems score	1.57 (1.98)	1.58 (1.82)
Total problems score	21.10 (11.46)	20.16 (12.88)
Development (BSID-III)		
Cognitive score	11.64 (2.23)	11.94 (2.03)
Fine motor score	11.50 (2.65)	11.72 (2.61)
Gross motor score	9.67 (2.43)	9.74 (2.37)
	Intention to treat analyses (N=282)	
	Mean difference (95% CI)	**p value**
Child behaviour (CBCL)		
Internalising problems score	0.672 (-0.331; 1.675)	0.187
Externalising problems score	0.190 (-1.550; 1.931)	0.829
Sleep problems score	0.015 (-0.521; 0.552)	0.956
Total problems score	0.973 (-2.530; 4.476)	0.583
Development (BSID-III)		
Cognitive score	-0.315 (-0.887; 0.258)	0.280
Fine motor score	-0.235 (-1.050; 0.580)	0.569
Gross motor score	-0.067 (-0.831; 0.698)	0.863
	Per protocol analyses (N=226)	
	Adjusted mean difference (95% CI)	**p value**
Child behaviour (CBCL)		
Internalising problems score	0.803 (-0.214; 1.821)	0.120
Externalising problems score	0.097 (-1.752; 1.946)	0.917
Sleep problems score	0.036 (-0.649; 0.722)	0.916
Total problems score	0.906 (-2.848; 4.659)	0.633
Development (BSID-III)		
Cognitive score	-0.367 (-0.964; 0.230)	0.227
Fine motor score	-0.354 (-1.209; 0.501)	0.413
Gross motor score	-0.025 (-0.924; 0.873)	0.955

Differences between groups are using linear regression and are adjusted for age, parity, socio-economic status and present diagnosis where appropriate. Missing values were imputed using multiple imputation by chained equations.

Discussion

The present study found no evidence of a beneficial effect of antenatal CBT in women with at least moderate levels of anxiety and/or depressive symptoms for the offspring at 18 months, as compared to CAU. Both the amount of behavioural and emotional problems as well as the child's cognitive, fine and gross motor development did not differ between the two groups.

The present study investigated the effects of antenatal CBT in women with at least moderate levels of anxiety and/or depressive symptoms on offspring behaviour problems and development at age 18 months, compared to CAU. We showed small but not statistically significant effects of CBT on the internalising, externalising, sleep problems and total problems scales of the CBCL and the cognitive, fine motor and gross motor scales on the BSID-III, as compared to CAU.

Limitations of our study include the low participation rate of women who were invited to participate in the trial. Only 28% of the eligible women agreed to participate in our intervention trial. Our response rate was somewhat low when compared to that of other similar studies that included pregnant women who were not active help-seekers. The study of Austin et al., that included pregnant women with subclinical symptoms or anxiety and depressive disorders, showed a slightly higher response rate of 39%.[82] The study by Le et al. that included women with subclinical symptoms or a previous depression had an even higher response rate of 70%.[81] On the other hand, strengths of this study should be mentioned. To our knowledge, this study is the first RCT investigating the effect of CBT during pregnancy on offspring mental health outcomes. We included a population-based sample that may allow us to generalise our findings to a larger Dutch pregnant population presenting with anxiety and/or depressive symptoms, as opposed to if we had recruited a sample from clinical settings only. Our response rate was fairly high and we used multiple imputation in dealing with missing values. This is considered more reliable than solely complete case analyses.[224] Furthermore, we used the widely validated Structured Clinical Interview for DSM-VI Disorders (SCID-I) to assess the presence of an anxiety or depressive disorder according to the DSM-VI and a manualised CBT intervention utilised by trained CBT psychologists to increase reliability.

In current international guidelines, together with antidepressants of which adverse perinatal effects are increasingly studied, CBT is the preferred treatment option for anxiety and depression although evidence for the effectiveness of CBT during pregnancy on offspring behaviour and development is sparse.[73-76] It is believed that CBT has a positive effect on maternal symptoms and furthermore may discourage the acknowledged adverse effects of antenatal psychopathology on offspring mental health. Accordingly, we hypothesised that CBT in pregnant women with at least

moderate levels of anxiety and/or depressive symptoms would have a positive effect on both offspring behaviour and development, as compared to CAU. However, our study did not show any effects of the provided CBT intervention.

A recent meta-analysis of studies investigating the effects of treatment of parental depression on offspring behavioural and cognitive problems concluded that there is no evidence of improvement of children's behaviour and development. Also a recent Pakistani RCT showed no effect of antenatal CBT on offspring cognitive, socio-emotional, or physical development at age 7. This study only assessed parent-reported child development and did not investigate effects on offspring behavioural problems.[87] However, our study extends this conclusion to both behavioural and emotional problems as well as the child's cognitive, fine and gross motor development, as measured by trained research assistants using the widely known BSID-III.

Nevertheless, it is still possible that CBT has a positive effect on the offspring when provided to women with more severe symptoms of anxiety and depression. As earlier published, our CBT intervention had no effect on antenatal symptom levels of anxiety and depression when compared to CAU.[237] In our sample, we included a population-based sample with mainly moderate symptom levels. Beneficial effects of decreasing these symptom levels to normal low levels are probably less than when provided to women with higher symptom levels. Another explanation may be that the beneficial effect of CBT was weaker than expected and that these could not be shown using this sample size. Future research should therefore include a larger sample of pregnant women with higher symptom levels to assess long-term effects of CBT on offspring mental health.

CHAPTER 11

General discussion

T. Verbeek

This thesis aimed to provide more knowledge of risk factors, long-term effects and treatment of anxiety and depression around pregnancy. We tested the following hypotheses:

1. Both the number of prior negative life events and aspects of low socio-economic status are positively associated with symptoms of anxiety and depression during pregnancy and with perinatal outcomes **(chapter 3)**.
2. The associations of the number of prior negative life events with symptoms of anxiety and depression during pregnancy and with perinatal outcomes are negatively modified by aspects of socio-economic status **(chapter 3)**.
3. In the Central American developing country Nicaragua, both the prevalence and the severity of anxiety and depression during pregnancy are higher than in developed countries **(chapter 4)**.
4. Both symptom levels of anxiety and depression and personality traits are independently associated with meeting the World Health Organisation (WHO)-recommendation of six months exclusive breastfeeding; the latter association is mediated by symptoms of anxiety and depression **(chapter 5)**.
5. Postnatal depression is associated with internalising and externalising mental health problems in the offspring during adolescence, independently of parental lifetime psychopathology **(chapter 6)**.
6. Treatment of anxiety and depression during pregnancy using cognitive behavioural therapy leads to a stronger reduction in these symptoms **(chapter 8)** and more favourable perinatal outcomes **(chapter 9)**, child development and child behaviour **(chapter 10)** as compared to care as usual.

After a summary of the main findings of this thesis follows a discussion of methodological issues that need to be considered before interpreting our findings. Finally, implications for clinical practice and recommendations for further research are provided.

Main findings

In **chapter 2**, screening and treatment of psychopathology during pregnancy in two women were described. The cases made clear how relevant early screening and treatment of symptoms of anxiety and depression are around pregnancy. Awareness and screening, followed by timely referral to a POP (psychiatry, obstetrics, and paediatrics)-team, may lead to more effective treatment, which may reduce or even prevent harmful consequences for all family members.

The first and second hypotheses were partly confirmed in **chapter 3**. Corresponding to present literature,[46,47] we found that the number of

negative life events was positively associated with symptoms of anxiety and depression during pregnancy. This association increased in magnitude when the events happened more recently, except for the negative life events in the first 16 years of life (child traumas). These results were similar to those of studies among non-pregnant populations.[49,50]

Furthermore, we found that maternal aspects of low socio-economic status (SES): low maternal educational level, maternal unemployment, and low family income were positively associated with symptoms of anxiety and depression during pregnancy. The associations of low SES with antenatal depression and anxiety have been shown earlier,[46-48] although literature was conflicting about which aspects of SES play a role. Remarkably we did not see any association for educational level and employment status of the partner. Although maternal and paternal anxiety and depression frequently correlate,[102] we did not find any literature on the association of paternal educational level and employment status on maternal anxiety or depression, but apparently these aspects of family SES have no impact on maternal psychopathology during pregnancy.

Associations of negative life events with adverse perinatal outcomes were observed in large population based studies (low birth weight: N=9,350, preterm birth: N=17,285).[56,57] This also applied to the adverse effect of low SES on obstetric outcomes.[58] In our study we found comparable trends, although not statistically significant, possibly due to the smaller sample size.

We found that the above-mentioned maternal aspects of low SES were not only positively associated with symptoms of anxiety and depression during pregnancy but that these also modified the effects of negative life events, significantly increasing them. When we repeated these analyses for perinatal outcomes, birth weight and gestational age, results showed similar trends, although they were mostly not statistically significant.

The third hypothesis was confirmed in **chapter 4**, wherein we presented that the prevalences of at least mild symptoms of anxiety and depression in our Nicaragua study were substantially higher than in our Dutch PAD-study. Furthermore, the severity of anxiety and depression, measured as mean symptom scores, were significantly higher in Nicaragua.

With respect to the burden imposed by mental disorders, mental health is known to be an under-researched health area, especially during pregnancy.[116] Although the WHO recognises psychopathology as an important global health problem, which causes morbidity and mortality in both mother and child, the problem may be even bigger than earlier thought.[14,59,60,93,104] Most earlier published prevalences of depression and/or anxiety during pregnancy were found in developed countries and were lower compared to those we found in our Nicaraguan sample, namely 10-15%.[2,47,105]

Literature demonstrating prevalences of antenatal anxiety and depression in developing countries outside Central America showed variable results.[114,116-118] The prevalences of anxiety (41%) and depression (57%) in our sample of Nicaraguan pregnant women were comparable to these earlier studies in developing countries but notably higher than in developed countries.

A very small proportion of the women, less than ten percent, indicated that psychological help was available and that they knew how to reach that help. This statement was associated with higher anxiety scores but not with higher depression scores, suggesting that anxious women may know how to find psychological help.

In **chapter 5**, we partly confirmed our fourth hypothesis. We found associations of both the symptom levels of depression during and after pregnancy and the personality trait of openness with meeting the World Health Organisation (WHO) recommendation of six months exclusive breastfeeding. The latter was only partly explained by symptom levels of anxiety and depression. Therefore, mediation of this association may be largely caused by a direct effect of the openness personality trait on continuation of breastfeeding.

Earlier studies on the association of personality traits with breastfeeding initiation in the United States (n = 87) [66] and with breastfeeding duration in the United Kingdom (n = 602) [67,68] showed associations between high conscientiousness,[67,68] high extraversion,[66,67,68] low neuroticism,[67,68] and high openness [66] with breastfeeding. After adjustment for symptoms of anxiety and depression, we only found a significant association of high openness with reaching the WHO recommendation of providing six months exclusive breastfeeding. Our findings suggest that women who succeed in providing breast milk for six months might be more open to new experiences and appear to be more outgoing, seeking novelty and variety.

Furthermore, earlier studies on different subjects suggested that openness influences the processes of receiving information and decision-making. Individuals who showed high scores in openness found it easier to accept information and were more prone to choose the options for protection than people with other dominant personality traits.[134,135] Thus, women with high levels of openness may accept information about breastfeeding more easily, and may be more likely to opt for protection of their infant than women with lower levels of openness. This may explain why women with higher scales of openness are more likely to meet the WHO recommendation.

Additionally, we found that personality traits were associated with anxiety and depressive symptoms around pregnancy. The latter findings are in line with earlier research conducted both in pregnant women[71,72] and in the general population.[69,70] However, earlier research was somewhat inconclusive about which trait is associated with psychopathology. In our

sample, low agreeableness, low conscientiousness, low extraversion, high neuroticism and high openness were associated with symptoms of both anxiety and depression during pregnancy and postpartum. In a recent meta-analysis the associations between personality traits of the five-factor model and risk of depressive symptoms were assessed in the general population.[69] Our results correspond with theirs, suggesting that the associations between personality traits with both anxiety and depression symptoms are similar in the case of both pregnant and non-pregnant women.

Also the fifth hypothesis was partly confirmed. As described in **chapter 6**, we found that postnatal depression is associated with mental health problems in the offspring during adolescence. The relationship appeared to be specific for internalising problems because there was no association with externalising problems. Parental psychopathology did not fully explain this association, suggesting at least a partly direct psychological effect on the child postpartum.

Earlier studies have indicated that postpartum depression may increase the risk of emotional and behavioural problems in early childhood.[29,33-37,150,153] However, there is debate whether negative effects of postpartum depression are lasting and extend into adolescence and what these effects are.[37,40-44] A commonly recognised limitation was the absence of correction for parental lifetime history of psychopathology, thus leaving the possibility that the association is due to liability shared by mother and offspring.[41] In our study we have overcome these limitations by correcting for dimension-specific parental loading for psychopathology. The observation that in our study the association between postpartum depression and internalising problems held up after adjustment for parental internalising psychopathology outside the postpartum period pleads for a direct psychological effect of postpartum depression. Such a direct psychological effect may be the result of impaired mother–child interaction, which has shown to lead to suboptimal attachment.[29,47,150,152,153] Alternative explanations of the association of postpartum depression with mental health problems in the offspring include neglect or even abuse of the child[172] or reduced frequency of breastfeeding.[173]

The sixth hypothesis was threefold, corresponding to three chapters relating to the randomised controlled trial we performed as described in **chapter 7**.

In **chapter 8**, we showed no significant differences between the group of women who received cognitive behavioural therapy, and the group of women who received care as usual. Thus, we could not confirm that cognitive behavioural therapy leads to a stronger reduction of anxiety and depressive symptoms at 36 weeks of gestation, as compared to care as usual.

Our results are somewhat surprising because there is strong evidence that cognitive behavioural therapy is effective in treating anxiety and depressive symptoms outside pregnancy.[47,59] However, recent studies presented that the

efficacy of both psychotherapy and pharmacotherapy may have been overestimated.[247,248] Our results are consistent with an earlier study on 277 women with anxiety and depressive symptoms/disorders wherein no beneficial effects of cognitive behavioural therapy were demonstrated.[82] Conversely, another study showed a significant decrease in antenatal depression symptom levels due to cognitive behavioural therapy among a sample of 217 Latina women with subclinical symptoms.[81] Finally, a small pilot study including 36 pregnant women with a depressive disorder compared a home-based cognitive behavioural therapy intervention with care as usual and also found a reduction in depression symptom levels in the therapy group, although not statistically significant.[80]

A major consideration in this trial is the observation that the mean levels of anxiety and depression symptoms were relatively low at screening. A substantial percentage of the women (127 of the 282; 45%) had subclinical symptoms, indicating that there may have been less room for improvement, i.e. further decline of symptom levels. Nevertheless, when assessing women with clinical symptoms only, no beneficial effects of cognitive behavioural therapy were demonstrated either. Unexpectedly, anxiety and depression symptom levels were increased in the group receiving cognitive behavioural therapy relative to the women who received care as usual, although this difference was not statistically significant.

Additionally, as studied in **chapter 9**, we observed no differences in both birth weight and gestational age between both groups overall. However, in participants with a present DSM-IV anxiety diagnosis, we found that the mean birth weight was over 275 grams lower and the mean gestational age approximately a week lower in the cognitive behavioural therapy group, as compared to care as usual. Our per-protocol analyses, wherein perinatal outcomes of women who received at least six CBT sessions were compared with women who received CAU, demonstrated an even stronger association. These adverse effects could not be explained by use of antidepressants or benzodiazepines, higher proportions of induced labour or caesarean section, smoking, or symptom levels of depression, but may partly be explained by the anxiety symptom level during pregnancy, which was increased in the group receiving cognitive behavioural therapy relative to the women who received CAU.

Although scarcely studied, very limited literature suggests that cognitive behavioural therapy may have adverse (side) effects.[242] Providing cognitive behavioural therapy for anxiety symptoms on the one hand treats symptoms, but on the other hand confirms that there are symptoms and the (expected) exposure increases anxiety in the short term, that these are disadvantageous, and that these should be treated.[243] The latter thoughts may increase anxiety symptoms, instead of decreasing them. As mentioned earlier, our mediation analysis shows that the difference in birth weight between both groups is

partly mediated by anxiety symptom levels at 24 weeks of pregnancy. In our CBT treatment, this is the moment when women receive their first sessions.

Consequently, we propose that the demonstrated adverse effects may be due to increased stress levels, conceivably induced by the provided CBT. Indeed, the dialogues and exposure during the sessions in CBT may be confrontational and may induce stress in the short-term, instead of reducing stress levels. Our per-protocol analyses demonstrated even stronger adverse effects, suggesting an exposure-response mechanism: the more CBT sessions the women received, the worse the perinatal outcomes.

Finally, in **chapter 10**, our preliminary results (child behaviour N=168, child development N=175) show no differences in behavioural and developmental problems or cognitive, fine and gross motor development in the offspring at 18 months of age.

A recent Pakistani randomised controlled trial showed no effect of antenatal cognitive behaviour therapy on offspring cognitive, socio-emotional, or physical development at age 7. However, this study only assessed parent-reported child development and did not investigate effects on offspring behavioural problems.[87] Nevertheless, our study extends this conclusion to both behavioural and emotional problems as well as the child's cognitive, fine and gross motor development, as measured by trained research assistants using the widely known Bayley Scales of Infant and Toddler Development, Third Edition.

Methodological considerations

The research presented in this thesis focuses on quantifying associations between exposure to risk factor(s) or treatment and clinical outcomes. In every clinical epidemiological study, interpretation of associations should be preceded by an evaluation of potential bias. Three types of bias should be distinguished: information bias, selection bias, and confounding.[249] The next paragraphs will discuss an evaluation of the potential of these types of bias, as well as the precision of our findings.

Information bias

One of the considerations regarding this thesis is the use of questionnaires, which have been used in almost all analyses. These questionnaires come with their typical limitations, i.e. misclassification and the potential for information bias.

For example, in **chapter 3**, negative life events were documented using retrospective self-report checklists, which may have been prone to recall bias through its potential link with symptoms of anxiety and depression at the

time of the assessments. Indeed, when people are anxious or depressed, they may think about adverse life experiences more often than people without symptoms of anxiety or depression. Additionally, in **chapter 6**, recall bias may have played a role in identifying cases of postpartum depression. Nevertheless, as mentioned earlier, retrospectively assessed adverse experiences, such as postpartum depression, do involve false negatives but rarely involve false positives.[174] Thus, in our study it is quite likely that those women who did report a postpartum depression actually had suffered a postpartum depression while an unknown number of women who actually suffered a postpartum depression did not report it. Consequently, the association between maternal postpartum depression and psychopathology may have been diluted by non-differential determinant misclassification, i.e. recall of postpartum depression was assumed to be independent of the presence of the adolescents' mental health problems. Therefore, the real association may be stronger than we observed. In **chapter 5**, we assessed exclusive breastfeeding at six months postpartum, as recommended by the WHO. It is not inconceivable that women give socially desirable answers, i.e. to answer positively to this question while they actually did not provide exclusive breastfeeding for six months. For this reason, it may be expected that the neuroticism personality trait, which is a trait characterised by anxiety and vulnerability, was a priori more likely to be associated with the WHO recommendation. Conversely, in our sample the openness to experience personality trait was associated with six months exclusive breastfeeding. A so-called self-serving bias was therefore less likely to have occurred.

Throughout the thesis, symptom levels of anxiety and depression were measured using widely recognised questionnaires. The Spielberger State Trait Anxiety Inventory (STAI) was used to assess symptom levels of anxiety.[95] In each analysis, we used the 6-item short-form to measure anxiety symptom levels which produces scores similar to those obtained using the full-form. The cut-off score for an at least moderate level of anxiety is >42.[95] This commonly used questionnaire has a good internal consistency (average Cronbach's alpha of .89).[111] The 10-item Edinburgh Postnatal Depression Scale (EPDS) was used to measure depression symptom levels.[96] The cut-off score for an at least moderate level of depression is ≥12. The 10-item EPDS has shown good internal validity with a Cronbach's Alpha of 0.82.[112] The used versions of the STAI and the EPDS have both shown to be valid during and after pregnancy.[95,96] A limitation is that both are self-report questionnaires and only measure symptom levels, so no diagnosis could be made. On the other hand, assessments of symptom levels are able to show smaller changes and thus may be more precise. Additionally, in Part II, we performed the widely validated Structured Clinical Interview for DSM-VI Disorders (SCID-II) to assess the presence of an anxiety and/or depressive disorder according to the DSM-IV.[204]

In the Nicaragua study, we were not able to perform a SCID interview, thus in **chapter 4** our analyses were limited to data from questionnaires. Even though the STAI and EPDS are commonly used worldwide, misunderstandings of the questionnaires, possibly due to illiteracy, may have led to over- or underreporting. As demonstrated in earlier research, a lower educational level is associated with a higher rate of psychopathology during pregnancy.[46] Nevertheless, when a participating woman was illiterate, we read the questionnaire aloud. We believed this was a better method then excluding all illiterate women. Additionally, our analyses showed similar results in both illiterate and literate women. Furthermore, cut-off values for both STAI and EPDS questionnaires may depend on different cultural backgrounds. However, since this is the first study among Nicaraguan women, we considered it justified to use the widely recognised cut-off values for an at least moderate level of anxiety and depression, as mentioned above.

As mentioned in **chapter 6**, the parental loadings for psychopathology used in the analyses in that chapter were rough approximations of genetic loading, since these measurements necessarily include (shared) environmental risk for decreased mental health as well. Methodologically, it would be more refined to report distinct effects of both genetic loading and environmental risk factors. However, research showed that the genetic basis for the intergenerational transmission of depression is not (yet) identified[250] and that shared environmental risk factors make important contributions to most forms of child and adolescence psychopathology.[251] Thus, currently it is impossible to measure separate effects of genetic loading and environmental effects. Nevertheless, the results of the analyses showed that the association of postpartum depression with internalising mental health problems remained statistically significant after correction for parental loading for lifetime internalising mental health problems. Thus, independent of both genetic loading and (shared) environmental risk for decreased mental health, postpartum depression has shown to have an adverse effect on the offspring, even in adolescence.

The most important finding in **chapter 9** is, apart from the absence of an advantageous overall effect, the adverse effect of cognitive behavioural therapy on both birth weight and gestational age in participants with a present DSM-IV anxiety diagnosis. Post-hoc exploratory mediation analyses showed that this adverse effect on birth weight but not on gestational age was partly (22.6%) mediated by anxiety symptoms at 24 weeks of gestational age. In our treatment, this was the moment when women received their first therapy sessions. Consequently, we propose that the demonstrated adverse effects may be due to increased stress levels, conceivably induced by the provided cognitive behavioural therapy. Indeed, the dialogs and exposure sessions, using imagery and rescripting, may be confrontational and may induce stress at short-term, instead of reducing stress levels. Our per-protocol analyses, wherein perinatal outcomes of women who received at least six therapy sessions were compared with women who received care as

usual, demonstrated even stronger adverse effects, suggesting an exposure-response mechanism: the more therapy sessions the women received, the worse the perinatal outcomes. An important limitation in this chapter is that we did not measure any biological stress markers during pregnancy. An increase in physiological stress measures, such as cortisol levels, (nor)adrenal hormones or other biological parameters could have provided us with more information about the mediators of the observed effects.

In **chapter 10**, we assessed effects of antenatal cognitive behavioural therapy for anxiety and depression on offspring behaviour problems and development at age 18 months, compared to care as usual. We showed small but not statistically significant effects of cognitive behavioural therapy on child behaviour problems and cognitive, fine motor and gross motor development, as compared to care as usual.

Behavioural and developmental problems were assessed using the Child Behaviour Check List for children of age 1.5 to 5 (CBCL 1.5–5) including the Caregiver-Teacher Report form (C-TRF).[208] This well established, reliable and valid scale comprises seven syndrome scales: emotionally reactive, anxious depressed, somatic complaints, withdrawn, sleep problems, attention problems and aggressive problems. In addition, it contains scales for internalising, externalising and total problems. Symptom scores may further be related to formal DSM-diagnostic criteria. The CBCL 1.5-5 is considered a sensitive instrument also deployed in several earlier studies.[211,212] For the assessment of psychopathology in preschool children it is considered essential to obtain information from different sources.[209] Therefore we decided to include the C-TRF for both the parents and the caregivers of the children other than their parents. Parents were instructed to hand these lists to the actual other caregivers of their children, e.g. grandparents, babysitters, kindergarten-coaches, etc. This methodology was intended to minimise misclassification and information bias.

Cognitive, fine and gross motor development levels were assessed using the Bayley III Scales of Infant and Toddler Development (BSID-III).[205] It was individually administered and consisted of three subscales: cognitive development (mental development index), gross and fine motor development. This tool is widely used in both research and clinical settings and is considered the best and most applied method for the assessment of the child's development to date.[206] Importantly, the instrument has shown to be sensitive. In the context of our study, maternal anxiety in pregnancy explained as much as 11% of the variance in the Bayley scores in a study among two-year-old toddlers.[207] All participating women received invitations for the BSID-III when their offspring were aged 18 months. Tests were performed in hospitals or at participant's homes. Trained research assistants masked to study group provided the cognitive and motor scales. Inter-observer variance was limited by providing supervision after reviewing and reassessing videotaped BSID-III assessments.

Selection bias

Some of the potential limitations of practically every population-based study are the risks of selective recruitment by researchers or healthcare providers and self-selection bias due, for example to low willingness to participate in the study. The strategies to handle this risk differed between the cohorts.

In the main TRAILS cohort, as described in **chapter 6**, there was no selective recruitment at personal level, because recruitment involved municipalities, which provided names and addressed of all eligible inhabitants. Because the recruitment of participants in the TRAILS-CC cohort involved all children who have been referred at least once to the child psychiatric outpatient clinic of the University Medical Center Groningen at any point in their life, there was no selective recruitment either. Selection bias due to willingness of participation was assessed by testing differences between responders and non-responders. Teacher-rated problem behaviour and socio-demographic variables were used in the TRAILS cohort[159] and psychopathology subscales, language performance, and demographic variables in the TRAILS-CC cohort.[158] There were no significant differences between responders and non-responders, suggesting that a selection bias was unlikely.[158,159]

In the Nicaraguan cohort, as described in **chapter 4**, we invited all women visiting one of the participating community health centres or the participating hospital for regular pregnancy consultations or in the final phase of pregnancy. Of the 105 eligible women, 98 (93%) women were willing to participate. This high participation rate decreases the possibility of a noticeable selection bias.

In the Pregnancy Anxiety and Depression (PAD)-study, as studied in **chapters 3-5**, all pregnant women in their first trimester of pregnancy visiting a total of 109 collaborating primary obstetric care centres and 9 hospitals in the Netherlands were invited to participate. It should be noted as a limitation that, due to logistical reasons, it has been impossible to determine how many women have actually been invited and consequently to determine the exact participation rate. Because the number of participating women was considerably lower than expected we conducted a survey among participating midwives and gynaecologists.[252] The results indicated that time constraints were mostly deemed responsible and that they had not specifically invited women they suspected to have risk factors, psychopathology or other conditions. Therefore, we have no reason to believe that responders and non-responders differed in any considerable way with respect to characteristics relevant to the present study. In other words, we do not believe that there was a relevant selection bias.

A potential limitation of PROMISES-study as described in the chapters in **Part II** of this thesis is the low participation rate of women who were invited to participate in the trial. Only 282 (28%) of the 1007 eligible women agreed to participate in our randomised controlled trial. Our response rate was somewhat low when compared to that of other similar studies that included pregnant women who were not active help-seekers. The study of Austin et al., that included pregnant women with subclinical symptoms or anxiety and depressive disorders, showed a slightly higher response rate of 39%.[82] The randomised controlled trial by Le et al. that included women with subclinical symptoms or a previous depression had an even higher response rate of 70%.[81] In our study, of the 239 women who declared the reason of non-participation in the trial, 160 (67%) were not interested in participating in a trial: they wanted to either have or have not therapy, but did not want to be randomised. Twenty-eight (12%) women addressed practical issues, e.g. they expected to have no time for therapy sessions, had to care for other children or had to work. The remaining 51 (21%) did not acknowledge their symptoms and/or felt no need for therapy. A selection bias due to low willingness to participate in this trial may have occurred, possibly an explanation of the low symptom levels of the participants, compared to earlier studies. After randomisation, an additional total of 15 women who were randomised to the group that would receive cognitive behavioural therapy, eventually refused therapy. Although literature states that women seem to have a preference for psychological therapy over antidepressants,[83] our figures suggest that at least a proportion of these women do not want cognitive behavioural therapy.

Confounding

Confounding is a type of bias which may occur in observational research. A confounding variable is linked to both the presumed determinant and the outcome and may interrupt a causal relation. By adding possible confounders to a regression analysis, it is possible to correct for confounding, leading to more valid results. Resulting from the nature of an observational study, correction for confounding is only possible for known variables.

For example, in **chapter 4**, we evaluated the differences in anxiety symptom level scores between Nicaragua and the Netherlands. The scores were remarkably higher in Nicaragua and while one of the possible differences between the two cohorts is that in the developing country of Nicaragua women experience more negative life events than women in the Netherlands. However, the low SES of Nicaraguan women compared to Dutch women may be the underlying cause of their symptomatology. Low socio-economic status may lead to both negative life events and psychopathology. Another possibility is that low SES may lead to negative life events, which may increase the risk of psychopathology. The first can be assessed by adding SES as independent variable to the regression analysis between negative life events and psychopathology. The latter can be assessed using a mediation

analysis.[239,240] Unfortunately, this study was only an explorative study and did not assess possible explanations for the high symptom level scores, such as negative life events.

As discussed in **chapter 1**, earlier research in the association between antenatal psychopathology and adverse effects in the offspring may be causal or non-causal. Causal effects may be divided into direct, e.g. foetal programming, and indirect, e.g. more smoking and less breastfeeding. A non-causal explanation may be a shared genetic or environmental predisposition by mother and child. Because all earlier research on this topic is observational, this confounding bias by genetics or environment could not be excluded. In our research in Part II of this thesis, we aimed on overcoming this bias by performing a randomised controlled trial wherein we attempted to lower the anxiety and/or depression symptom levels in one group and compare outcomes to the other group. In the event of observing positive effects on symptom levels, i.e. lower levels in the cognitive behaviour therapy group when compared to the care as usual group (positive maternal effects), and of observing positive effects on perinatal, behaviour and/or cognitive (offspring) outcomes, we should have concluded that a causal explanation was more likely. In contrast, in the event of observing positive maternal effects but no offspring outcomes, a causal explanation was less likely. Unfortunately, no effects on maternal symptom levels were observed, thus we are not able to draw any conclusion on the causality issue.

Precision

Precision stands for the extent wherein results will be similar when the research is repeated, or in other words: the measurement of noise, and is inversely related to random error. In general: the greater the sample size, the smaller the noise, and the greater the precision. In all chapters, we considered $p<0.05$ as statistically significant, and we reported the corresponding 95% confidence intervals as well.

One issue relating to precision concerns the results of **chapter 9**. This chapter provides evidence for an adverse effect of CBT on perinatal outcomes when provided to pregnant women with a DSM-IV anxiety diagnosis. However, this is a subgroup analysis and not a trial wherein solely women with an anxiety diagnosis were included. Nevertheless, we believe that this study gives a strong indication that cognitive behavioural therapy has a possible adverse effect on the unborn child and therefore should not be provided to pregnant women with a DSM-IV anxiety diagnosis. Ideally, further research will be conducted on antenatal treatment options in women with anxiety disorders, wherein perinatal outcomes should be studied.

Implications for clinical practice and future research

The findings in this thesis add to the knowledge of risk factors, long-term effects and treatment of anxiety and depression during and after pregnancy. Overall, the findings in this thesis provide several implications for both (future) clinical practice and research.

Identification of personal characteristics

Modern health care is evolving: in history, medical practice was based on doctors' personal experience and opinion. This way of performing medicine is largely substituted by evidence-based medicine. In vitro studies, animal models, epidemiological studies and trials led to uniform diagnostic, prognostic and treatment guidelines. A limitation herein is that less attention may be paid to personal differences between patients. Indeed, due to limited resources, studies are performed on groups of patients, which are heterogeneous by definition because of participants' different individual characteristics. In the future, this 'group-based evidence' may be replaced by a more personalised medicine: taking the personal characteristics of the individual patient into account, healthcare providers may perform personalised medicine. Parts of this thesis may contribute to this way of providing this personalised healthcare.

As discussed in **chapter 2**, treatment of psychopathology in pregnant women may be complex and severe cases should be performed by a POP (psychiatry, obstetrics, paediatrics)-team. However, the general practitioner and the midwife should have a major role in screening of anxiety and depression in pregnant women. General practitioners mostly have a long-term relationship with their patients and know them well and therefore are acquainted with their patient's family history, socio-economic status (SES), major (negative) life events, as well as medical (psychiatric) history.

As summarised above, in **chapter 3**, both a low SES and a high number of negative life events may have an adverse effect on symptomatology of anxiety and depression during pregnancy. An implication of the findings may be that more attention should be paid to the assessments of both negative life events and earlier mentioned aspects of SES in designing and implementing psychosocial interventions for pregnant women. Interventions are presumably most cost-effective when targeted at women with a low SES and with a history of multiple life events, in particular those who have experienced child traumas or recent events, because in that group the greatest advantage may be gained.

In **chapter 5**, we studied personality traits, symptoms of anxiety and depression and its association with exclusive breastfeeding, which has well-known health benefits for both mother and child. Our analyses show an

association of both the openness personality trait and symptoms of depression during pregnancy with exclusive breastfeeding for six months, as recommended by the WHO. The resulting advice to midwives, general practitioners and other maternal healthcare providers should be both to screen for symptoms of depression and to determine the personality traits of all pregnant women.

In the contemporary daily practice, it is uncommon to assess personal features as number of negative life events, SES, or personality. Additionally, in study settings personality is mostly assessed using questionnaires but this is highly unusual in clinical practice. Therefore, unless personality traits are assessed using shorter screeners, it is unlikely that this study will imply that above-mentioned maternal healthcare providers will integrate such questionnaires into their daily practice. Nevertheless, these chapters add to our understanding of interpersonal differences in the risk of anxiety and depression during pregnancy and in the chance of fulfilling the WHO breastfeeding recommendation. Furthermore, when personalised evidence-based medicine will become more common, the results as described in this chapter may help healthcare providers to decide which of their patients may need extra attention to fulfil the recommended breastfeeding results. In the future, new technological innovations may support screening in medical practice. For example, using online platforms, risk stratification may become easier, more reliable and less time-consuming during the consultation.

Antenatal psychopathology in Central America

The results of **chapter 4**, as summarised above, strongly suggest the need for further research. Compared to developed countries, lower education, lower income, younger maternal age, and more negative or traumatic life events could be factors in the Central American country Nicaragua that relate to a higher risk of suffering from psychopathology during pregnancy.[46,59]

The WHO reported that in Nicaragua only 1% of the total health care budget is reserved for mental health, and 91% of that is given to psychiatric hospitals.[106] Under these circumstances, it is likely that relatively mild mental health issues in a specific population such as pregnant women are neglected. Psychological help may not be commonly available for the women in the rural areas, therefore in addition to more knowledge about the problems, the possibilities of providing effective treatment if needed, e.g. psychotherapy for antenatal psychopathology, should be explored. It would be desirable to investigate the results of this possible solution in a follow-up study in the same geographical area.

Effects of postpartum depression on offspring

In **chapter 6**, we demonstrated that postnatal depression is associated with internalising but not with externalising mental health problems in the offspring during adolescence and that this association is only partially explained by parental lifetime psychopathology. Therefore, mediation of this association may be largely caused by a direct psychological effect on the child in the postpartum period, e.g. as a result of impaired mother–child attachment. Early screening for and treatment of maternal postpartum depression may decrease her depressive symptoms[175-177] and, if the association appears causal, may thereby prevent internalising psychopathology in the offspring, ultimately in adolescence.[178] In addition, because particularly early management of psychopathology in adolescence may reduce symptoms,[179,180] the offspring of mothers with a history of postpartum depression could be monitored more closely for internalising problems in early adolescence.

Treatment of antenatal psychopathology using cognitive behavioural therapy

In **part II** of this thesis, the effects of cognitive behavioural therapy for anxiety and depression during pregnancy were assessed. In contrast of what is suggested by current international guidelines,[73-76] this thesis demonstrates no advantageous effect on maternal symptom level during pregnancy (**chapter 8**), perinatal outcomes (**chapter 9**), behavioural and emotional problems or the child's development (**chapter 10**).

The results of **chapter 8** imply that other interventions than cognitive behavioural therapy should be studied. Patient engagement seems to be a predictor of greater reductions in interventions on both anxiety and depressive symptoms.[226] Thorough explanation of the sense of therapy, leading to increase of motivation, but not to increase stress, may be helpful. Additionally, less intensive interventions, e.g. relaxation therapy, support, and internet-based interventions, combined with screening tools to acknowledge undesirable increases in anxiety, depression or stress levels should be explored as therapy for subclinical symptoms.

Furthermore, **chapter 9** showed that cognitive behavioural therapy may not only have no positive effects on major perinatal outcomes, but in fact may have an adverse effect, when provided as early treatment in pregnant women with a DSM-IV anxiety diagnosis. Additionally, in pregnant women with a DSM-IV depression diagnosis, or without any DSM-IV diagnosis, no positive effects on perinatal outcomes were observed. Therefore, although antenatal cognitive behavioural therapy is most likely to be effective for prevention of postpartum depression, this therapy should not be provided as prevention of low birth weight or prematurity in women and should be reconsidered as

antenatal treatment of anxiety symptoms in the light of possible long-term adverse effects of both low birth weight and low gestational age.[253]

Our daily medical practice is as much as possible founded on research (evidence-based medicine), wherein a meta-analysis of multiple randomised controlled trials is considered as the highest level of evidence. However, due to ethical concerns on performing research on pregnant women, to date the effectivity of anxiolytics and antidepressants during pregnancy has not been evaluated. The results of our trial in Part II of this chapter provides evidence for an adverse effect of CBT on perinatal outcomes when provided to pregnant women with a DSM-IV anxiety diagnosis. However, this is a subgroup analysis and not a trial wherein only women with an anxiety diagnosis were included. Nevertheless, we believe that this study gives a strong indication that cognitive behavioural therapy has an adverse effect on the unborn child and therefore should not be provided to pregnant women with a DSM-IV anxiety diagnosis. Preferably, further research will be conducted on antenatal treatment options in women with anxiety disorders, wherein perinatal outcomes should be studied. Additionally, future studies could explore potential underlying biological mechanisms and possible long-term effects of cognitive behavioural therapy during pregnancy on the offspring, which in **chapter 10** of this thesis have not been demonstrated. Nevertheless, ethical concerns in performing a trial using a possibly harmful treatment in pregnant women should be taken into account.

Earlier research in general population settings showed cognitive behavioural therapy to have unremitting positive effects in treating anxiety and depression.[46,59] In the light of both this research and the findings in this thesis, it may be recommended that women of fertile age should be screened for (risk factors of) anxiety and depression and, when desired, treated using cognitive behavioural therapy before, but not during pregnancy.

Conclusion

Psychopathology during and after pregnancy is an important personal and public health problem with adverse consequences for mother and child in both the short term (e.g. lower probability to exclusively breastfeed for six months) and the long term (e.g. higher change of offspring mental health problems during adolescence). In Central America, anxiety and depression during pregnancy is highly prevalent and symptom levels are more severe than in developed countries. Low-income women who recently or as a child experienced negative life events are more likely to develop symptoms of anxiety and depression. Conversely, cognitive behaviour therapy as a treatment for subclinical psychopathology should not be provided during pregnancy because of the absence of positive maternal and child developmental effects and the presence of possible adverse effects on perinatal outcomes.

SUMMARY / SAMENVATTING

Pregnancy and Psychopathology

For a lot of people, because of the joy and happiness of a new life, pregnancy means being on cloud nine. The general population may not be aware that this does not apply to every woman. Psychopathology during and after pregnancy should not be underrated. For as much as 10-20% of all pregnant women, pregnancy results in black clouds, gathering over them.

This thesis will discuss different aspects of psychopathology and pregnancy. Consequences of anxiety and depression for the offspring will be discussed, as well as risk factors. In the first part of this thesis (**chapters 2-6**), studies in the Netherlands and abroad will shed light on these topics. In the second part (**chapters 7-10**), effects of treatment of antenatal anxiety and depression using cognitive behavioural therapy on symptom level, perinatal outcomes, child development, and child behaviour as compared to care as usual will be discussed.

In **chapter 2**, screening and treatment of psychopathology during pregnancy in two women were described. The cases made clear how relevant early screening and treatment of symptoms of anxiety and depression are during and after pregnancy. Awareness and screening, followed by early referral to a POP (psychiatry, obstetrics, and paediatrics)-team, may lead to a more effective treatment, which may reduce or even prevent harmful consequences for all family members.

In **chapter 3**, we demonstrated that the number of negative life events was positively associated with symptoms of anxiety and depression during pregnancy. This association increases when the events happened more recently, except for the negative life events in the first 16 years of life (child traumas). Furthermore, we found that maternal aspects of low socio-economic status: low maternal educational level, maternal unemployment, and low family income, not only were positively associated with symptoms of anxiety and depression during pregnancy but that these actually increased the adverse effects of negative life events. Our analyses of obstetric outcomes, birth weight and gestational age, showed similar trends, although these were mostly not statistically significant.

In **chapter 4**, we presented that the prevalence of at least mild symptoms of anxiety and depression in our Nicaraguan study was three times as high as in our Dutch PAD-study for anxiety and for depression even higher at almost ten times. Furthermore, the severity of anxiety and depression, measured as mean symptom scores, were significantly higher in Nicaragua. However, only one in every ten women indicated that professional psychological help was available.

In **chapter 5**, we showed associations of both the symptom levels of depression during and after pregnancy and the personality trait of openness with meeting the World Health Organisation (WHO)-recommendation of six months exclusive breastfeeding. The latter was only partly explained by

symptom levels of anxiety and depression. Additionally, we found that the high personality traits of agreeableness, conscientiousness and extraversion and low traits of neuroticism and openness were associated with symptoms of both anxiety and depression during pregnancy and in the postpartum period.

In **chapter 6**, we demonstrated that postnatal depression is associated with internalising mental health problems in the offspring during adolescence. The relationship appeared to be specific for internalising problems because there was no association with externalising problems. Parental psychopathology did not fully explain this association, suggesting at least a partly direct psychological effect on the child postpartum.

In **chapter 7**, we provided a detailed description of our randomised controlled trial where we assessed the effects of cognitive behavioural therapy provided to pregnant women with at least moderate symptoms of anxiety and/or depression, on maternal antenatal symptom level, perinatal outcomes and behavioural and developmental problems or cognitive, fine and gross motor development in the offspring at 18 months of age, as compared to care as usual.

In **chapter 8**, we demonstrated that symptom levels of anxiety and depression decreased during pregnancy but we showed no differences between the group of women who received cognitive behavioural therapy, and the group of women who received care as usual. Thus, we could not confirm that cognitive behavioural therapy leads to a stronger reduction of anxiety and depressive symptoms at 36 weeks of gestation, as compared to care as usual.

Additionally, as studied in **chapter 9**, we observed no differences in both birth weight and gestational age between both groups. However, in participants with a present DSM-IV anxiety diagnosis, we found that the mean birth weight was over 275 grams lower and the mean gestational age almost a week lower in the cognitive behavioural therapy group, as compared to care as usual. These adverse effects may partly be explained by the anxiety symptom level during pregnancy, which was increased in the CBT group relative to the women who received CAU.

Furthermore, in **chapter 10**, our preliminary results show no differences in behavioural and developmental problems or cognitive, fine and gross motor development in the offspring at 18 months of age.

In conclusion, psychopathology during and after pregnancy is an important personal and public health problem with adverse consequences for mother and child on both short term (e.g. lower probability to exclusively breastfeed for six months) and long term (e.g. higher change of offspring mental health problems during adolescence). Screening and treatment should be targeted

at low-income women who recently experienced negative life events, both in the Netherlands as in Central-America. Conversely, treatment for subclinical psychopathology should not be provided during pregnancy because of the absence of positive maternal and child developmental effects and the presence of possible adverse effects on perinatal outcomes.

Voor veel mensen geldt de zwangerschap als een mooie en blijde periode, vanwege de hoop op en verwachting van een nieuw leven. Zij zitten spreekwoordelijk op een roze wolk. Veel mensen zijn zich er niet van bewust dat dit niet voor iedere vrouw geldt. Psychische klachten tijdens en na de zwangerschap moet niet worden onderschat. Voor zo'n 10 tot 20% van alle zwangere vrouwen geldt dat er zwaar weer op komst is.

Dit proefschrift omhelst verschillende aspecten van psychopathologie rondom de zwangerschap. Gevolgen van angst en depressie op het nageslacht worden onderzocht, naast diverse risicofactoren. In het eerste deel van het proefschrift (**hoofdstukken 2-6**) worden deze onderwerpen besproken middels studies binnen en buiten Nederland. In het tweede deel (**hoofdstukken 7-10**) worden de effecten van behandeling van angst en depressie tijdens de zwangerschap op maternale symptomen, perinatale uitkomsten, ontwikkeling en gedrag van het kind vergeleken met de reguliere zorg.

In **hoofdstuk 2** wordt de screening en behandeling van psychische problematiek rondom de zwangerschap geïllustreerd aan de hand van twee casusbeschrijvingen. Deze maken duidelijk hoe relevant screening en vroegtijdige behandeling zijn tijdens en na de zwangerschap. Systematische screening, gevolgd door een laagdrempelige verwijzing naar een POP (psychiatrie, obstetrie en pediatrie)-team, kan leiden tot een meer effectieve monitoring en behandeling van psychische klachten. Uiteindelijk kan dit de nadelige gevolgen voor alle gezinsleden verminderen of zelfs voorkomen.

In **hoofdstuk 3** laten we zien dat het aantal negatieve levensgebeurtenissen positief is gerelateerd aan de hoeveelheid symptomen van angst en depressie tijdens de zwangerschap. Deze associatie is sterker wanneer de levensgebeurtenis korter geleden is gebeurd, al geldt dit niet voor de gebeurtenissen in de eerste zestien levensjaren (zogenaamde jeugdtrauma's). Daarnaast zagen we dat de aan de moeder gerelateerde aspecten van de socio-economische status, namelijk: laag opleidingsniveau van de moeder, werkloosheid van de moeder en een laag gezinsinkomen, waren gerelateerd aan angst en depressie. Bovendien hadden deze aspecten invloed ook invloed op de associatie van het aantal negatieve levensgebeurtenissen met angst en depressie tijdens de zwangerschap: hoe lager het socio-economische niveau, hoe sterker het effect van de levensgebeurtenissen was op de hoeveelheid symptomen. We hebben deze associaties ook onderzocht met geboortegewicht en zwangerschapsduur als uitkomstmaat en hierin zagen we dezelfde trends, al waren deze niet statistisch significant.

In **hoofdstuk 4** presenteren we dat de prevalentie van op zijn minst matige symptomen van angst in ons Nicaraguaanse cohort driemaal zo hoog was als in ons Nederlandse cohort en voor symptomen van depressie zelfs tienmaal zo hoog. Bovendien was de ernst van de symptomen van angst en depressie statistisch significant hoger in Nicaragua. Desalniettemin gaf slechts een op

de tien Nicaraguaanse vrouwen aan dat er psychologische hulp beschikbaar is voor hen.

In **hoofdstuk 5** laten we zien dat zowel de symptoomniveaus van angst en depressie tijdens en na de zwangerschap als de persoonlijkheidstrek 'openheid' onafhankelijk van elkaar zijn gerelateerd aan het geven van borstvoeding zonder bijvoeding (exclusieve borstvoeding) gedurende een halfjaar na de bevalling, zoals het advies is van de Wereldgezondheidsorganisatie (World Health Organisation; WHO). Ook zagen we dat de persoonlijkheidstrekken altruïsme, consciëntieusheid en extraversie positief zijn geassocieerd met symptomen van zowel angst als depressie rondom de zwangerschap en dat neuroticisme en openheid hiermee juist negatief zijn geassocieerd.

In **hoofdstuk 6** demonstreren we dat postnatale depressie is geassocieerd met internaliserende psychische problematiek bij het nageslacht, zelfs wanneer dit de puberteit heeft bereikt. Dit lijkt niet te gelden voor externaliserende psychische problematiek. Deze associatie kon niet geheel worden verklaard door psychische problemen bij de ouders, wat suggereert dat een postnatale depressie een gedeeltelijk direct effect heeft op langdurige psychische problemen bij het kind.

In **hoofdstuk 7** wordt ons gerandomiseerd onderzoek met controlegroep (randomised controlled trial; RCT) beschreven. Hierin hebben we de effecten van cognitieve gedragstherapie voor zwangere vrouwen met op zijn minst matige symptomen van angst en/of depressie op maternale symptomen; perinatale uitkomsten; cognitieve, grof- en fijnmotorische ontwikkeling en gedrag van het kind op 18 maanden na de geboorte vergeleken met de reguliere zorg.

In **hoofdstuk 8** beschrijven we dat in onze studie de symptoomniveaus van angst en depressie afnemen , maar dat er geen verschillen worden gevonden tussen de groep die cognitieve gedragstherapie krijgt en de groep die de reguliere zorg ontvangt. Hierdoor konden we niet bevestigen dat cognitieve gedragstherapie leidt tot een sterkere afname van symptomen van angst en depressie na 36 weken zwangerschap.

In **hoofdstuk 10** laten we zien dat er ook geen verschillen werden gezien tussen de beide groepen, in geboortegewicht of zwangerschapsduur. Echter, in de groep met deelneemsters met een diagnose die onder de DSM-IV classificatie van angst valt, zagen we dat het gemiddelde geboortegewicht meer dan 275 gram lager was en de gemiddelde zwangerschapsduur ongeveer een week korter was, wanneer zij cognitieve gedragstherapie kregen. Deze nadelige effecten zouden verklaard kunnen worden doordat het angstniveau tijdens de zwangerschap hoger was, mogelijk als gevolg van de confronterende technieken tijdens de psychotherapie.

Tenslotte presenteren we in **hoofdstuk 10** de voorlopige resultaten van de uitkomsten op cognitieve, grof- en fijnmotorische ontwikkeling en gedrag van het kind op 18 maanden na de geboorte. Hierin worden geen verschillen gevonden tussen de kinderen van de deelneemsters die therapie kregen en van de deelneemsters die de gebruikelijke zorg ontvingen.

Concluderend, psychopathologie tijdens en na de zwangerschap is een belangrijk gezondheidsprobleem op zowel persoonlijk als maatschappelijk vlak. De psychische problemen hebben gevolgen voor moeder en kind, op zowel korte termijn (zoals een kleinere kans op het geven van zes maanden exclusieve borstvoeding) en lange termijn (zoals een grotere kans op psychische problemen in de puberteit). Screening zou moeten worden gericht op vrouwen met een laag socio-economisch niveau die recentelijk negatieve levensgebeurtenissen hebben meegemaakt, zowel in Nederland als in Central-Amerika. Desalniettemin zou cognitieve gedragstherapie als behandeling van subklinische psychopathologie niet moeten worden gegeven, vanwege het ontbreken van een positief effect op maternale symptomen en kindontwikkeling en -gedrag en de mogelijk nadelige effecten op perinatale uitkomsten.

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OVER DE AUTEUR

Curriculum vitae

Tjitte Verbeek werd op 23 mei 1988 geboren in het Friese dorpje Warns. Na enkele jaren verhuisde hij naar Wommels, waar hij opgroeide met zijn ouders en zijn twee zusjes. In hetzelfde dorp ging hij naar de openbare basisschool De Opslach. Hij behaalde in 2006 zijn gymnasiumdiploma aan de RSG Magister Alvinus te Sneek, waarna hij in hetzelfde jaar startte met de studie Geneeskunde aan de Rijksuniversiteit Groningen.

In de hierop volgende jaren participeerde hij in diverse extracurriculaire activiteiten, onder meer als voorzitter van de jaarvertegenwoordiging en als lid van de onderwijs & onderzoeksraad. Ook was hij betrokken bij de oprichting van het studententraject tot het behalen van een basiskwalificatie onderwijs, waarna hij dit traject zelf doorliep. Vanaf het tweede jaar tot aan het einde van zijn studie werkte hij in de praktijk van huisarts J.W.A. van Willigen. Daarnaast voerde Tjitte in het derde jaar zijn JSM-proefproject uit bij dr. H. Burger op de afdeling Epidemiologie, wat als startpunt voor een langdurige samenwerking zou dienen.

Na het met 'honours' behalen van zijn bachelordiploma rondde Tjitte met goed gevolg zijn stage wetenschap af en startte hij in 2010 met zijn MD/PhD-traject, in combinatie met de opleiding tot Epidemioloog. Hij doorliep zijn coschappen in het Martini ziekenhuis te Groningen en het Medisch Centrum Leeuwarden, met als een van de hoogtepunten een driemaandelijks verblijf in Nicaragua samen met Joep Vendrik. Vervolgens liep Tjitte zijn semi-artsstages op de afdeling obstetrie & gynaecologie van het Nij Smellinghe ziekenhuis te Drachten en de afdelingen kindergeneeskunde & neonatologie van het Children's Hospital of Philadelphia, Pennsylvania, VS.

Sinds zijn terugkomst uit de VS werkt Tjitte als arts-assistent op de spoedeisende hulp van het Scheper ziekenhuis te Emmen. Hoewel Tjitte onverminderd is geïnteresseerd in de gynaecologie & obstetrie heeft de huisartsgeneeskunde zijn hart gestolen. Hij hoop dan ook in 2016 te starten met zijn opleiding tot huisarts en deze opleiding te combineren met een post-doc positie gericht op innovatie in de eerstelijns gezondheidszorg.

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